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SERUM SELENIUM CONCENTRATIONS IN PATIENTS WITH NEWLY DIAGNOSED LYMPHOID MALIGNANCIES

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ABSTRACT

Background. **Increased mortality from lymphoid malignancies following exposure to environmental selenium has recently been reported. Moreover, conflicting results have been found in investigations examining the relationship between serum concentrations of selenium and some clinical features of malignant lymphoproliferative diseases.**

Methods. **Serum concentrations of selenium were analyzed by atomic absorption spectrometry in fifty-nine patients with newly diagnosed chronic lymphoid malignancies and in forty control subjects**

Results. **Selenium concentrations were significantly lower in patients than in control subjects. However, when only patients with localized disease were compared to controls, no significant difference in serum selenium concentrations was observed. Clinical stage was inversely associated with selenium levels. High-grade non-Hodgkin's lymphoma was characterized by lower selenium levels than low-grade and intermediate-grade disease. Selenium levels were positively associated with albumin and hemoglobin, and inversely correlated with serum concentrations of _-2-microglobulin and with erythrocyte sedimentation rate.**

Conclusions. **The findings of this study do not suggest that a high selenium intake represents a risk factor for malignant lymphoproliferative diseases, but limitations of the investigation hamper evaluation of the results. The possible utility of determining serum concentrations of selenium in the clinical evaluation of patients with lymphoid malignancies merits examination in larger studies.**

Key words: selenium, serum, lymphoproliferative disorders, Hodgkin's disease; non-Hodgkin's lymphoma, multiple myeloma, chronic lymphocytic leukemia, neoplasms

Much scientific attention is currently focused on the possible role of selenium as an antineoplastic drug and the hypothetical involvement of this trace element in the etiology of human cancer. Great interest has been shown for some of the effects that pharmacological doses of selenium have on cell proliferation and viability, suggesting the possible use of selenium compounds as antineoplastic drugs.[1,2] The serious toxicity of several selenium compounds, which seems to be strictly related to the carcinostatic and cytotoxic activity of these compounds,[3] however, hampers their consideration in clinical practice. The epidemiologic evidence linking selenium exposure to human cancer appears inconsistent, due to the conflicting results of recent ecologic investigations[4-6] and case-control studies with both cross-sectional and prospective design.[7,8] In fact, no association, an inverse one and a direct association between selenium exposure and cancer have been observed in these investigations. A

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tendency toward a positive association between selenium intake and the subsequent incidence of cancer has recently been reported in a large cohort-nested case-control study.[9]

Neoplasms of the lymphoid system represent one of the most frequently examined site-specific cancers in case-control studies with cross-sectional design for analyzing the possible relationship between serum concentrations of selenium and cancer,[10-16] but the results of these studies have been conflicting. In two investigations a tendency toward higher selenium levels in patients with reticuloendothelial neoplasms[10] and with Hodgkin's disease[11] was observed, whereas significantly low serum concentrations of selenium were reported in patients affected by chronic lymphocytic leukemia[12] and epidermotropic cutaneous T-cell lymphoma.[16] Moreover, different results were obtained in these studies regarding the association between selenium status and the clinical stage of the neoplasms.

In a recent cohort study examining cancer mortality following accidental exposure to hexavalent selenium through drinking water, a higher mortality from non-Hodgkin's lymphoma and lymphoid malignancies was seen in females.[17] Moreover, in a cohort of Baltic Sea fishermen, a higher mortality from multiple myeloma was observed in subjects whose diets provide a significant supplementation of selenium as well as other nutrients and pollutants.[18]

These observations led us to examine the serum levels of selenium in patients with newly diagnosed lymphoid malignancies and the possible association between the levels of this trace element and some clinical features of the disease.

Materials and Methods

A consecutive series of fifty-nine patients with suspected or newly diagnosed chronic lymphoid malignancies (Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma and chronic lymphocytic leukemia) referred to the Hematology Service of S. Maria Nuova Hospital in Reggio Emilia, northern Italy, were enrolled in the study. None of the patients had been previously treated.

Venous blood drawn in the morning after overnight fasting was 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. In four cases, diagnosis of malignant lymphoproliferative disease was not confirmed, and these subjects were removed from the investigation. Eight of the patients included in the study (4 males and 4 females) were affected by Hodgkin's disease, 39 (27 males and 12 females) by non-Hodgkin's lymphoma, 7 (5 males and 2 females) by multiple myeloma and 5 (2 males and 3 females) by chronic lymphocytic leukemia.

The following hematologic parameters were also determined in several patients: erythrocyte sedimentation rate, hemoglobin, serum levels of albumin, β2-microglobulin, serum lactate dehydrogenase and copper.

Four general practitioners from the Local Health Unit in Reggio Emilia were asked to select a sample of the individuals on their rolls. Forty controls, 17 males and 23 females, agreed to participate in the study following an invitation from their family doctors and were referred to the Hematology Service. Blood samples from these individuals were obtained following the same procedures used in the patients.

Serum selenium was determined at the Laboratory of Industrial Toxicology of the Department of Occupational Health of Scandiano, Reggio Emilia, using atomic absorption spectrometry.[19] A graphite furnace Perkin-Elmer 4100ZL atomic absorption spectrometer with background Zeeman correction was used for the analyses. Determinations were made in duplicate, and the analysts were blinded as to the case status of the specimens.

Spearmans rank correlation analysis was used to examine the relationship between serum selenium levels and age in the study population, and between selenium and the remaining hematologic variables in patients. Unpaired Student's t-test, analysis of variance and analysis of covariance were used for comparisons between means. A two-tailed p-value of less than 0.05 was considered significant in all procedures. The statistical analyses were carried out using the SPSS/PC+ software.

Results

Selenium concentrations were 92.3±13.6 μg/L in control subjects (100.2±12 μg/L in males and 86.5±11.8 μg/L in females) and 82.6±15.5 μg/L (83.6±15.5 μg/L in males and 80.6±15.6 μg/L in females) in patients with lymphoid malignancies ($p<0.05$ vs. controls - Table 1). The difference in selenium concentrations between males and females was statistically significant in control subjects ($p=0.001$) but not in patients ($p=0.479$). In control subjects, age was not significantly correlated with serum selenium ($p=0.759$), whereas a significant inverse correlation was observed in patients ($p=0.002$). Serum concentrations of selenium in the different lymphoid malignancies are shown in Table 1. In comparison with controls, the serum levels of selenium were significantly lower in patients with non-Hodgkin's lymphoma ($p<0.05$) and multiple myeloma ($p<0.001$). Further adjustment for gender in the statistical analysis made the differences between controls and patients with non-Hodgkin's lymphoma significant at a p-level<0.001.

Serum selenium concentrations according to clinical stage in patients with non-Hodgkin's lymphoma are shown in Table 2. These concentrations were inversely associated with stage, and statistically significant differences were observed between patients with stage IV and stage I lymphoma. Results did not change significantly after adjustment for gender. Levels of selenium in stage I-II lymphomas were not significantly different from the values observed in control subjects, whereas selenium concentrations in stage IV disease were significantly lower than in with controls ($p<0.001$). A tendency toward lower levels of selenium in patients with more advanced disease was also observed in Hodgkins disease, multiple myeloma and chronic lymphocytic leukemia. In subjects with Hodgkins disease, selenium concentrations were 96.8±6, 90.3±4.7 and 75.7 μg/L, respectively, in patients with stage I (n=3), stage II (n=4) and stage III (n=1) disease.

In patients with non-Hodgkin's lymphoma, serum selenium was higher in intermediate-grade and lower in high-grade disease in comparison with low-grade disease (Table 3). Differences among the three groups were not statistically significant, but when clinical stage was included in the analysis as a confounder, a p-value of 0.003 was obtained. After adjustment for stage, selenium in patients with high-grade lymphoma was not significantly lower than in patients with low-grade disease ($p=0.054$), whereas the difference between high-grade and intermediate-grade disease was statistically significant ($p<0.001$). The difference in serum selenium concentrations between subjects with low-grade lymphoma and intermediate-grade disease was not statistically significant ($p=0.119$). The presence of systemic symptoms in non-Hodgkin's lymphoma and Hodgkin's disease was not associated with significant differences in selenium concentrations with respect to patients without these symptoms. The level of selenium in the thirty-five patients with non-Hodgkins lymphoma reporting the presence of systemic symptoms was 83.7±15.2 μg/L, while in the remaining four patients with lymphoma not reporting systemic symptoms selenium

Table 1. Serum selenium levels (mean value1SD) in control subjects and in patients with lymphoid malignancies.

	n	*age (yr)*	*selenium (μg/L)*
control subjects	40	50.0±14.5	92.3±13.6
lymphoid malignancies	59	58.4±15.7*	82.6±15.5*
Hodgkin's disease	8	35.9±8.9*	90.9±8.2
non-Hodgkin's lymphoma	39	60.8±14.5*	83.2±14.9*
multiple myeloma	7	65.3±10.7*	69.1±18.8°
chronic lymphocytic leukemia	5	65.8±4.9*	83.2±15.8

**p<0.05 vs. control subjects; °p<0.001 vs. control subjects*

Table 2. Serum selenium levels in patients with non-Hodgkin's lymphoma according to clinical stage of the disease. Results are expressed as mean 1SD (number of subjects).

	selenium (μg/L)
non-Hodgkin's lymphoma:	
stage 1	95.8±15.4 (9)
stage 2	89.4±7.4 (6)
stage 4	76.9±12.7 (24)*°

**p<0.001 vs. control subjects; °p=0.001 vs. patients with stage 1 disease.*

Table 3. Serum selenium concentrations (µg/L) in patients with non-Hodgkin's lymphoma according to grade of the disease. Results are expressed as mean1SD (n)

	low grade	*intermediate grade*	*high grade*	*p**	*p°*
selenium levels	80.7±11.7(17)	87.7±16.6(17)	76.3±17.1(5)	0.515	0.003
adjusted[#] selenium levels	84.8	90.8	69.1		

**p-value at analysis of variance among the diagnostic groups; °p-value at analysis of variance among the diagnostic groups adjusting for clinical stage; [#]adjusted for clinical stage.*

Table 4. Correlation between serum selenium concentrations and hematologic parameters in patients with non-Hodgkin's lymphoma.*

	S°	*p-value*
albumin	0.413	0.011
β2-microglobulin	–0.471	0.018
lactate-dehydrogenase	–0.270	0.123
copper	–0.030	0.869
erythrocyte sedimentation rate	–0.410	0.012
hemoglobin	0.376	0.018

**determinations were available in 37 patients for albumin, in 25 for β2-microglobulin, in 34 for lactate dehydrogenase, in 32 for copper, in 37 for erythrocyte sedimentation rate and in 39 for hemoglobin; °Spearman's rank correlation coefficient.*

concentrations were 78.9±12.8 5 g/L (p=0.55).

In patients with lymphoid malignancies, selenium levels correlated positively with albumin and hemoglobin, whereas an inverse association with erythrocyte sedimentation rate and β2-microglobulin was observed. Serum levels of copper and lactate dehydrogenase did not correlate with selenium concentrations. When analysis was restricted to patients with non-Hodgkin's lymphoma (Table 4), the results did not change significantly.

Discussion

In the present study, patients with newly diagnosed malignant lymphoproliferative diseases were found to have lower serum selenium levels than control subjects, but this difference was entirely due to the low selenium concentrations in patients with advanced disease. The findings of the study are in accordance with observations made in chronic lymphocytic leukemia[13] and in epidermotropic cutaneous T-cell lymphoma,[16] which show a tendency for serum selenium levels to decrease 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. In two other investigations which examined the relationship between the stage of lymphoid malignancies and serum selenium concentrations,[11,12] no apparent association was observed, and serum selenium levels in the whole patient group were not significantly different from the values observed in controls. Most of the patients examined in one of these investigations, however, had already received treatment for the disease.[11] The influence of therapy on serum selenium levels in lymphoid malignancies is controversial since it has been associated with either increased[11] to normal[12] serum selenium concentrations. It has been suggested that chemotherapy or radiotherapy might increase the release of selenium into the blood from the neoplastic tissue,[10,11] which (as will be discussed later) has, at least in some types of tumors, a higher selenium content than the remaining tissues.[20-23]

The inverse association between progression of lymphoid malignancies and selenium status observed in the present study is consistent with previous observations in patients with cancer,[24-27] although not all studies concur.[28,29] 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. This hypothesis, however, was not tested in the present study or in previous investigations, to the best of our knowledge. In the patients with Hodgkin's disease and lymphoma examined in this study, however, no association was observed between selenium status and the presence of systemic symptoms, which might also have been linked to changes in dietary habits. 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 neo-

plastic tissues in a variety of human and animal tumors.[20-23,30-34] This phenomenon, which has been specifically examined in patients with Hodgkin's disease and non-Hodgkin's lymphoma and in animal models of lymphoma,[30,32-34] represents the basis for the clinical use of labelled 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 that preferential uptake of labelled selenium compounds decreases following tumor irradiation,[35] 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.[11]

The association observed in the present study between the grade of non-Hodgkin's lymphoma and selenium status suggests that high-grade lymphomas are linked to the lowest serum concentrations of the trace element. The number of patients with high-grade lymphoma, however, was very low and therefore these results must be evaluated with caution, especially since serum levels of selenium were higher in patients with intermediate-grade lymphoma than in those with low-grade disease. A tendency toward higher selenium concentrations in patients with well-differentiated lymphoid malignancies and non-Hodgkin's lymphoma has been reported.[11,12] The absence in the present study of a relationship between serum selenium levels and the presence of systemic symptoms in patients with Hodgkins disease and lymphoma confirms previous reports.[12]

In agreement with observations in patients with cancer and other diseases,[13,36,37] but unlike what was found in a group of patients with reticuloendothelial tumors,[11] a significant correlation between selenium levels and albumin was detected in the overall patient group as well as in the group with non-Hodgkin's lymphoma. 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.[38] A variation in albumin and selenium independently induced by the progression of the lymphoid neoplasm might also be hypothesized. The association between hemoglobin and serum selenium observed in the present study in patients with non-Hodgkin's lymphoma was not supported in a previous investigation.[11] No other study, to our knowledge, has analyzed a possible association between selenium levels and erythrocyte sedimentation rate, serum levels of lactate dehydrogenase, copper and β2-microglobulin in patients with non-Hodgkin's lymphoma. The inverse correlation of erythrocyte sedimentation rate and β2-microglobulin with selenium found in this investigation deserves to be analyzed in larger studies.

Since in the present work a relationship was observed between serum selenium levels and hematologic parameters, stage and, in non-Hodgkin's lymphoma, grade, it seems appropriate to examine the possible utility of determining selenium status in the clinical evaluation of patients with lymphoid malignancies. Larger studies however are required to evaluate this possibility. Moreover, selenium status markers at clinical onset of a lymphoproliferative malignancy might represent a prognostic factor of the disease, as recently suggested in epidermotropic cutaneous T-cell lymphoma.[16] Serum levels of selenium should therefore be considered for inclusion in future follow-up studies together with the prognostic factors identified so far or suggested in Hodgkins disease[39] and lymphoma.[40] The patients with non-Hodgkins lymphoma examined in the present study have been entered in a follow-up in order to analyze the possible relationship between serum levels of selenium at diagnosis of the disease and response to chemiotherapy.

The findings of this study do not suggest that overexposure to selenium represents a risk factor for lymphoid malignancies since the levels of selenium in patients affected by stage I Hodgkin's disease and non-Hodgkin's lymphoma were only slightly elevated with respect to controls, whereas the number of patients affected by early-stage multiple myeloma and chronic lymphocytic leukemia was insufficient to yield meaningful data. Due to the cross-sectional design of the study, the above mentioned hypo-

thesis cannot be entirely ruled out however. In fact even in patients with localized disease, a disease-mediated decrease in serum selenium levels, a sensitive short-term marker of selenium intake and status,[41,42] cannot be excluded, and this interferes with our ability to establish positive association between selenium intake and lymphoid malignancies. 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[43] or tetravalent[44] 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. Nor do the results of the present study suggest that a low selenium status represents a risk factor for lymphoid malignancies, since the serum concentrations of selenium in patients with localized disease were no lower than those observed in controls. The results of this investigation do not however rule out a possible involvement of selenium in the etiology of lymphoid malignancies at intake levels considerably higher or lower than those typical of the Italian population examined in the study.

In conclusion, the results of the present study suggest that the serum concentration of selenium in newly diagnosed lymphoid malignancies is inversely associated with the clinical stage of the disease, but this relationship needs to be confirmed in larger studies. This investigation does not support the hypothesis of an involvement of high selenium intake in the etiology of malignant lymphoproliferative diseases, but the limitations of the study do not allow definitive conclusions to be drawn on this topic.

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