Reprint from
Trace Element – Analytical Chemistry in Medicine and Biology, Vol. 4
Editors: P. Brätter · Peter Schramel

CORRELATION OF SERUM TRACE ELEMENTS WITH OTHER BIOLOGICAL PARAMETERS IN HEMOPROLIFERATIVE DISORDERS

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Abstract

Serum trace elements were measured by PIXE in 88 patients with hemoproliferative disorders (Lymphoma, Hodgkin's disease, chronic lymphocytic leukemia, multiple myeloma, polycythemia vera and myeloproliferative disorders). Calcium, copper, zinc, selenium and bromine were correlated with other biological parameters, including hematocrit, WBC and platelet counts, ESR, fibrinogen, transferrin, ceruloplasmin, haptoglobin, orosomucoid, antitrypsin, serum protein, albumin, alpha 2-globulin, alkaline phosphatase, SGPT, LDH, gamma-GT, cholesterol, triglycerides, glycemia, urea, uric acid, creatinine, beta 2-microglobulin, CEA and C1q assay for circulating immune complexes. Copper was correlated with the different inflammatory tests (all P values < 0.01) and with the value of the C1q assay ($P < 0.001$). Zinc was inversely correlated with the inflammatory tests. The Cu/Zn ratio was thus significantly related to the importance of inflammation (all P values < 0.01). Calcium and zinc were correlated with albumin ($P < 0.05$). Selenium was positively correlated with gamma-GT ($P < 0.001$) and alkaline phosphatase ($P < 0.001$), and also with glycemia ($P < 0.001$). Bromine was not significantly associated with any other biological parameter. The significance of these associations is discussed.

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Introduction

There are few reports on serum trace element (STE) levels in hemopro-liferative disorders (HPD). Usually, serum copper levels are elevated and serum zinc levels are lowered in patients with active desease (1 - 10). Cu levels and Cu/Zn ratio might be useful parameters to monitor disease activity in patients treated for Hodgkin's disease (1, 2) or lymphoma (3, 4).

The present study was undertaken to measure serum calcium, copper. zinc, selenium and bromine in chronic HPD and to investigate the significance of the observed abnormalities in 88 patients. The STE values were correlated with a number of biological parameters to find out whether disease activity, inflammation, bone marrow, renal and hepatic functions or metabolic factors could significantly alter their levels in patients with HPD.

Patients and methods

88 patients with hemoproliferative disorders (HPD) were studied. There were 23 patients with multiple myeloma (MM), 13 with Hodgkin's disease (HD) or non-Hodgkin's lymphoma (NHL), 18 with chronic lymphocytic leukemia (CLL), 14 with polycythemia vera (PV) and 20 with myeloproliferative disorders (MPD). There were 56 males and32 females. Age ranged from 25 to 82 years. The patients were compared with a group of 100 healthy subjects.

Serum trace elements (STE) were measured by the PIXE method (Particle-Induced X-Ray Emission) (11), allowing for a simultaneous determination of calcium (Ca), copper (Cu), zinc (Zn), selenium (Se) and bromine (Br). The copper-to-zinc ratio (CZR) was calculated from the actual Cu and Zn levels.

At the same time as for STE determination, blood was drawn for the measurement of other biological parameters, including hematocrit, white blood cell (WBC) and platelet counts, erythrocyte sedimentation rate (ESR), fibrinogen, transferrin, ceruloplasmin, orosomucoid, haptoglobin, antitrypsin, serum protein and protein electrophoresis, alkaline phosphatase, serum glutamic pyruvic trans-

aminase (SGPT), gamma-glutamyl transferase (gamma-GT), total cholesterol, HDL cholesterol, triglycerides, glycemia, urea, uric acid, creatinine, beta 2-microglobulin, carcinoembryonic antigen (CEA) and C 1 q assay for circulating immune complexes.

Results

Mean STE levels for the 88 patients and for each diagnostic group are shown in Table 1. All the groups were characterized by decreased serum Ca ($P < 0.001$) and Zn ($P < 0.001$) levels and by increased Cu levels ($P < 0.001$), as compared to normal controls. Therefore, the CZR was significantly raised in patients ($P < 0.001$). Serum Se and Br levels in patients did not differ significantly from those found in controls.

Table 1
Mean STE levels in hemoproliferative disorders

Diagnosis	N	Ca	Se	Br	Cu	Zn	CZR
MM	23	96.2	0.095	4.63	1.23	0.85	1.48
NHL-HD	13	94.5	0.079	4.23	1.34	0.80	1.72
CLL	18	95.8	0.111	5.61	1.34	1.00	1.39
PV	14	94.4	0.072	5.39	1.26	0.99	1.32
MPD	20	95.8	0.099	4.91	1.30	0.96	1.42
TOTAL	88	95.5	0.094	4.96	1.29	0.92	1.45
CONTROLS	100	102.5	0.097	5.36	1.10	1.10	1.03

The values are given in µg/ml except for the CZR.
MM = Multiple Myeloma. NHL = Non-Hodgkin's Lymphoma.
HD = Hodgkin's Disease. CLL = Chronic Lymphocytic Leukemia.
PV = Polycythemia Vera. MPD=Myeloproliferative Disorders.

Table 2 displays the R correlation coefficients between STE and the other biological parameters. Only the statistically significant associations are shown. Ca ($P < 0.001$) and Zn ($P < 0.05$) were positively correlated with albumin. Se showed a direct relationship with gamma-GT ($P < 0.001$) and alkaline phosphatase ($P < 0.001$), but not with SGPT. Se was also correlated with glycemia ($P < 0.001$), but not with triglycerides nor cholesterol. Cu was significantly associated with the various inflammatory tests except with alpha 2-globulin.

Table 2

R correlation coefficients between STE and other biological parameters

	Ca	Se	Br	Cu	Zn	Cu/Zn
Hematocrit				-0.237°		-0.355*
Platelets	0.227°					
C1q assay			0.251°	0.379*		0.278°
ESR				0.265°	-0.283+	0.442*
Fibrinogen				0.329+	-0.221°	0.447*
æ1 antitrypsin				0.330+		0.307+
Ceruloplasmin				0.550*	-0.276+	0.628*
Orosomucoid				0.279+	-0.307+	0.422*
æ2-globulins					-0.255°	0.310+
Albumin	0.374*		0.230°		0.268°	
Alkalinephosphatase		0.387*		0.227°		0.224°
Gamma-GT		0.580*				
SGPT						0.244°
ß2 microglobulin					-0.249°	
Uric acid					-0.240°	
Glycemia		0.402*				
Triglycerides			-0.226°			
CEA		0.269°				
Bromine	0.250°					

R correlation coefficients not reaching statistical signifiance are not shown.
P values : °: $P < 0.05$ +: $P < 0.01$ *: $P < 0.001$

The strongest association was found to be the one with ceruloplasmin ($R = 0.550$, $P < 0.001$). Cu was also correlated with the value of the C1q assay ($P < 0.001$). Zn was inversely correlated with most of the inflammatory tests. The opposite effects of Cu and Zn accounted for the strong relationship between inflammation and the CZR. The CZR also bore an inverse relationship with the hematocrit ($P < 0.001$).

Discussion

The results of this study urge us to stress some problems of methodology in trace element research. The first problem would be the use of several samples taken from the same patient at different times, in order to increase sample size (1, 9). Repeated extrem values in a same patient may create some "highly significant" correlations (data not shown) and may considerably alter mean values. Another problem arises from weak but significant correlation coefficients between two parameters (Table 1). Figures with marginally significant P values should be interpreted very cautiously and be further investigated in larger studies before definitive conclusions can be drawn. Although HPD are diseases sharing many characteristics in common, there are important differences that may change the significance of some parameters from one disease to another. Therefore, some significant associations of STE with other biological parameters could be missed when amalgaming patients with different diagnosis. However, in a previous study (12), we found similar results among the different groups of patients with various HPD. The findings were confirmed in the present study (Table 1). Each group bore a similar pattern, i. e. decreased Zn and increased Cu levels, both being moderately but highly significantly altered. The elevation of the CZR was more impressive, perhaps to a larger extent in HD and NHL than in the other groups. Similar results have been reported by others for MM (6, 8, 9), NHL (3, 4, 6 - 9), HD (1, 2, 5- 1o) and CLL (6, 1O). However, the significance of these findings are difficult to assess and the mechanism may be multiple. Decreased serum Zn in HPD can be accounted for by anorexia and decreased Zn intake (13), tissue catabolism (14), antimetabolite drugs (13), and intercurrent infections

(13, 14). The role of the so-called leucocytic endogenous mediator (LEM) remains unclear (15). The increased Cu levels in cancer patients have often been considered as a consequence of ceruloplasmin production as part of a nonspecific acute phase reaction (3), but this assumption has been questionned by others (16).

Because we found a similar pattern of STE levels in the different HPD studied, we examined the significance of the observed anomalies in the entire group of 88 patients.

Decreased Zn and increased Cu levels represent, to a certain degree, disease activity in HPD. The inverse relationship between the CZR and the hematocrit also supports this idea. The elevation of serum Cu seemed to be largely due to an aspecific inflammatory process (3, 16). In this prospect, it was not surprising to find a strong association between ceruloplasmin and Cu. However, part if this inflammation could be caused by clinical or subclinical infectious episodes (13, 14).

Decreased Ca and Zn levels probably resulted from impaired balance between increased tissue catabolism and depressed food intake (13, 14). Serum Ca and Zn are normally mainly bound to albumin (17), and both were significantly correlated with serum albumin (Table 2). Zn deficiency may be responsible for the relative immunosuppression of patients with HPD (18 - 20). A number of studies have demonstrated that Zn deficiency impaired lymphocyte function (20,21) and that Zn supplementation could reverse immunosuppression induced by Zn deficiency (20) or by age (22).

The correlation between serum Se on one hand, and gamma-GT and alkaline phosphatase on the other hand, may be due to elevated VLDL levels in patients presenting some degree of cholestasis (17). However, we were enable to show any correlation between triglycerides and Se. This relationship seems to be on contradiction with reported Se deficiency in alcoholic subjects with or without liver disease (23). However, one cannot anticipate the result of liver damage in patients with presumable normal Se stores, from the situation of chronic selenium deficient alcoholics.

Although we found no siginificant association between triglycerides and Se, the relationship between Se and glycemia is to be compared to a recent report on elevated serum Se levels in diabetic children (24). This observation warrants further investigation.

Acknowledgements

We are indepted to the Institut Interuniversitaire des Sciences Nucléaires for financial support. We wish to express our thanks to the Centre de recherche du Cyclotron for its technical assistance.

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