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Serum copper and zinc concentrations in serum from patients with cancer and cardiovascular disease

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Abstract

A single cross-sectional study for serum copper and zinc levels was evaluated in 20 patients with cancer (respiratory, digestive, haematological, gynaecological) and 21 patients with cardiopathy (acute myocardial infarction and ischemic cardiomyopathy). A control group of 84 healthy subjects was selected. The mean serum zinc levels in patients with gynaecological cancer and ischemic cardiomyopathy were significantly lower than the control group ($P < 0.05$). However, the mean serum copper level was not statistically different among patients with cancer ($P > 0.05$) and cardiomyopathy ($P > 0.05$) than the control group. Male patients did not have statistically different values for serum Cu ($P > 0.05$) and Zn ($P > 0.05$) than those found in female patients. Patients' age did not have any statistical influence ($P > 0.05$) on serum Cu and Zn levels. © 1997 Elsevier Science B.V.

Keywords: Cardiopathy; Cancer; Copper; Zinc; Serum

1. Introduction

There is an increasing amount of available information about the possible coincidence and association of trace elements in the pathogenesis of cardiovascular diseases and malignant neoplasms. Copper and zinc are two important minerals that play important roles in a variety of biochemical reactions as cofactors of the superoxide dismutase (SOD) enzyme (Yücel et al., 1994). This enzyme plays an important role in the protection of the organism against free radicals and, conse-

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quently, prevents the initiation and progression of neoplastic events (Johnson et al., 1992).

Different epidemiological studies have individually shown the correlation of serum Cu and Zn levels with different pathologies which have been related to several types of cancer (Yücel et al., 1994; Linder, 1988; Jia, 1991; Ma and Jiang, 1993; Malvy et al., 1993; Yoshida et al., 1993), cardiovascular diseases and hypercholesterolemy (Klevay and Moore, 1990; Magalova et al., 1994; Arnaud et al., 1994; McGrath et al., 1995).

In this study we determined serum Cu and Zn concentrations in 41 patients with cancer ($n = 20$) and cardiovascular diseases ($n = 21$) from the southern part of the province of Granada (southeastern Spain). This single cross-sectional study was performed in order to provide useful information about the possible function of both minerals in the etiology of both diseases. Serum Cu and Zn concentrations were statistically compared with those previously determined in 84 healthy subjects (control group) (Terrés-Martos et al., 1997; Martín-Lagos et al., 1997) in order to observe whether trace element concentrations could be correlated with considered malignancies. In addition, the influence of the sex of patients in serum concentrations of both elements was considered.

Taking into account that the aging process normally implies jointly a change of Cu and Zn serum levels and an increase in serum Cu levels from 12–13 μmol/l in adolescents to 20 μmol/l in the elderly (Wright et al., 1995), we also studied the influence of age on serum Cu and Zn concentrations in patients with cancer and cardiovascular diseases.

2. Materials and methods

2.1. Subject selection

The study was carried out on a sample of 20 patients with cancer. This group was divided into four subgroups, according to tumor location (respiratory, digestive, haematological, gynaecological (breast, ovary, vesicle, urethra, prostate)). Similarly, 21 patients with cardiovascular diseases were examined; this group was also divided into two subgroups (with acute myocardial infarction and with ischemic cardiomyopathy). A group of 84 healthy subjects (control group) whose serum Cu and Zn levels were previously determined (Terrés-Martos et al., 1997; Martín-Lagos et al., 1997), were considered. According to their age, patients were divided into two groups (≤ 65 years old, > 65 years old).

2.2. Collection of serum samples

The release of human serum samples for analysis was approved by the Ethics Committee of the Hospital of Motril. Fasting blood samples were taken in the morning at the laboratory of clinical analyses of the Hospital of Motril following the procedure previously described (Terrés-Martos et al., 1997).

2.3. Analytical methods

Serum samples' mineralization was performed using an HNO_3-$HClO_4$ digestion procedure described elsewhere (Terrés-Martos et al., 1997; Martín-Lagos et al., 1997). Once the obtained digest was diluted to volume with ultrapure water, zinc and copper were determined by direct aspiration of the analytical dissolution into the flame of the atomic absorption spectrometer (Perkin-Elmer model 1100B). Copper and zinc hollow cathode lamps (Perkin-Elmer Corp., Norwalk, CT) were operated under the conditions recommended by the manufacturer. Spectral slit widths of 1.0 nm were selected to isolate the 324.7 and 213.9 nm lines for copper and zinc, respectively. All analyses were performed in peak height mode to calculate absorbance values. All samples were analyzed in triplicate.

Absorbance correlation obtained by the existing concentration of copper and zinc in the analyzed samples was carried out by the linear calibration method, after showing that matrix effects were negligible (Terrés-Martos et al., 1997; Martín-Lagos et al., 1997). Commercially available standard copper and zinc solutions (prepared from $Cu(NO_3)_2$ and $Zn(NO_3)_2$ in HNO_3 0.5 M,

respectively) were used to prepare by serial dilutions the standard solutions used for the calibration graph.

2.4. Accuracy and precision

The accuracy of the method was evaluated by recovery tests. Mean recoveries for the added samples were 104.7 and 102.7 for copper and zinc, respectively. Copper and zinc concentrations determined in the reference material (Trace Metal Serum Control A from the Kaulson Laboratories, Inc., NJ) were 0.98 ± 0.13 and 2.33 ± 0.49 mg/l, for certified values of 0.90 ± 0.15 and 2.37 ± 0.35 mg/l, respectively (Terrés-Martos et al., 1997; Martín-Lagos et al., 1997). Relative standard deviations for copper and zinc in the range of the samples analyzed in this study were better than 5 and 6%, respectively.

2.5. Statistical analysis

The results obtained are expressed as mean and standard deviation. In order to consider the influence of age and disease on the studied variables (serum copper and zinc levels), we used the Student's *t*-test, when the variables fulfilled the parametric conditions, and the Kruskall-Wallis test when these were non-parametric. The Kolmogorov-Smirnov test and the Bartlett test were used to check the normal distribution of variables and the homogeneity of variances, respectively. Association between variables was determined using the Pearson or the Spearman correlation coefficients, respectively (level of significance was set at 0.05). The statistical study was carried out using Statgraphics 6.0 Software Package (STSC, Inc.).

3. Results

Serum copper and zinc concentrations in patients with cancer and cardiovascular disease are shown in Table 1. Serum zinc mean levels were 0.73 ± 0.24 mg/l and 0.87 ± 0.35 mg/l in subjects with cancer and cardiovascular disease, respectively. Serum copper mean concentrations were 0.93 ± 0.33 mg/l and 1.02 ± 0.31 mg/l, respectively. Male patients did not present any statistically different serum copper and zinc levels ($P > 0.05$) than those found in females.

Table 2 shows serum copper and zinc concentrations from patients depending on their age (group I: ≤ 65 years; group II: > 65 years). No statistically significant differences were observed between both groups as regards the considered variables in patients with cardiovascular disease and cancer.

Table 3 shows mean concentrations, standard deviations and ranges corresponding to serum copper and zinc levels from patients grouped according to the type of cancer (respiratory, digestive, haematological, gynaecological), and healthy controls. The application of the ANOVA indicated that zinc concentrations in patients with cancer were significantly lower than those determined for healthy controls ($P = 0.024$). The multiple range test showed that patients with

Table 1
Serum copper and zinc concentrations in patients with cancer and cardiovascular diseases classified by sex

Disease	Sex	*n*	Zn (mg/l)		Cu (mg/l)	
			Mean ± S.D.	Range	Mean ± S.D.	Range
Cancer	M	9	0.72 ± 0.28^{a}	0.46–1.43	0.93 ± 0.33^{b}	0.44–1.66
	F	11	0.74 ± 0.22^{a}	0.52–1.21	1.12 ± 0.33^{b}	0.70–1.78
	All	20	0.73 ± 0.24	0.46–1.43	1.03 ± 0.33	0.44–1.78
Cardiovascular	M	18	0.87 ± 0.35^{c}	0.30–1.49	1.02 ± 0.31^{d}	0.65–1.66
	F	3	0.92 ± 0.05^{c}	0.88–0.98	1.41 ± 0.33^{d}	1.06–1.70
	All	21	0.88 ± 0.32	0.30–1.49	1.07 ± 0.33	0.65–1.70

[a,b,c,d]Not different statistically ($P > 0.05$).

Table 2
Serum copper and zinc levels in patients with cancer and cardiovascular diseases classified by age group

Disease	Age (years)	Zn ± S.D. (mg/l)	Cu ± S.D. (mg/l)
Cancer	≤ 65	0.91 ± 0.29[a]	1.06 ± 0.33[c]
	> 65	0.84 ± 0.36[a]	1.09 ± 0.36[c]
Cardiovascular	≤ 65	0.74 ± 0.20[b]	1.03 ± 0.43[d]
	> 65	0.71 ± 0.30[b]	1.09 ± 0.32[d]

[a,b,c,d]Not different statistically ($P > 0.05$).

gynaecological cancer presented Zn levels significantly lower than healthy individuals.

Mean concentrations, standard deviations and ranges corresponding to serum copper and zinc levels in patients grouped according to the type of cardiovascular disease (acute myocardial infarction or ischemic cardiomyopathy), and healthy controls are shown in Table 4. The application of the ANOVA indicated that Zn concentrations in patients with cardiopathies were significantly lower than those obtained for healthy controls ($P = 0.027$). The application of the multiple range test showed that patients with ischemic cardiopathy presented zinc levels significantly lower than the control group.

4. Discussion

4.1. Patients with cancer

4.1.1. Zinc

The multiple range test established that serum Zn mean concentrations in patients with gynaecological cancer (0.74 ± 0.22 mg/l) were significantly lower than those obtained for healthy controls (0.95 ± 0.25 mg/l) (Table 3; $P < 0.05$). In any case, it is important to notice that all groups of patients with different types of cancer presented lower mean Zn levels than the control group.

The word cancer is used to describe a wide group of diseases characterized by an uncontrolled proliferation of accidental tissues (Williams and Dickerson, 1990). In relation to zinc, during recent years many studies have been car-

Table 3
Serum copper and zinc levels in healthy controls and patients with cancer disease classified depending on the type of cancer

Subjects	Zn (mg/l)			Cu (mg/l)		
	n	Mean ± S.D.	Range	*n*	Mean ± S.D.	Range
Healthy controls	80	0.95 ± 0.25	0.42–1.54	84	1.10 ± 0.32	0.304–2.000
Respiratory cancer	1	0.62	—	1	1.00	—
Digestive cancer	6	0.73 ± 0.20	0.52–1.05	6	1.13 ± 0.30	0.848–1.656
Hemaetological cancer	6	0.73 ± 0.36	0.46–1.43	6	0.95 ± 0.41	0.440–1.648
Gynaecological cancer	7	0.74 ± 0.22*	0.53–1.21	7	1.04 ± 0.35	0.696–1.776

*$P < 0.05$.

Table 4
Serum copper and zinc levels in healthy controls and patients with cardiovascular disease classified depending on the type of disease

Subjects	Zn (mg/l)			Cu (mg/l)		
	n	Mean ± S.D.	Range	*n*	Mean ± S.D.	Range
Healthy controls	80	0.95 ± 0.25	0.42–1.54	84	1.10 ± 0.32	0.30–2.00
Myocardial infarction	12	1.00 ± 0.33	0.66–1.49	12	1.19 ± 0.34	0.86–1.70
Ischemic cardiopathy	9	0.71 ± 0.23*	0.30–0.98	9	0.92 ± 0.28	0.65–1.47

*$P < 0.05$.

ried out in order to determine the possible correlation of serum and body zinc levels with the incidence of the great variety of types of cancer that can develop in the human organism (Table 5). Although contradictory results have been observed in the zinc status in neoplasms, in most studies a decrease in plasma zinc levels has been observed. This fact is related to the advance of the disease. At the moment a protecting effect of zinc against cancer has been reported (Szymanska et al., 1991). It is probably due to the relation of this element with vitamin A when zinc activates the vitamin mobilization from the liver. This vitamin is involved in protection against free radicals and, therefore, in carcinogenic processes (Szymanska et al., 1991). Moreover, zinc together with copper are the two most important metals that play important roles in a variety of biochemical reactions as cofactors of the superoxide dismutase enzyme (Yücel et al., 1994; King and Keen, 1994) which also prevents the initiation and progression of neoplastic events by protecting the cells against the substance (anion superoxide) that causes the free radical formation (McGrath et al., 1995; Johnson and Fischer, 1992). Therefore, the low peripheral levels of zinc cannot be considered as carcinogenic promoters, but a decrease in the defense mechanisms of the organism during the development of the nutritional and metabolic disturbances, and inflammation processes related to cancer (Malvy et al., 1993).

Different studies related to breast cancer (Yücel et al., 1994; Gupta et al., 1991) and prostate cancer (Picurelli et al., 1991; Likili et al., 1991) showed significantly lower zinc levels in patients than in healthy controls (Table 5). This result is similar to that observed in this study in patients with gynaecological cancer.

Moreover, studies carried out by Kirpatrick et al. (1994) determined that the risk of suffering

Table 5
Serum or plasma zinc levels determined by other investigators in healthy subjects when compared with patients with cancer

Cancer	Country	Patients/controls	Zn (mg/l)	Significance	Reference
Brain	Japan	With meningioma	1.20 ± 0.08	NS[a]	(Yoshida et al., 1993)
	Japan	With mestatic carcinoma	1.04 ± 0.06	NS[a]	(Yoshida et al., 1993)
	Japan	With glioma	1.17 ± 0.04	NS[a]	(Yoshida et al., 1993)
	Japan	Controls	1.20 ± 0.08		(Yoshida et al., 1993)
Malignant	China	Patients	0.81	S[b]	(Jia, 1991)
	China	Controls	—		(Jia, 1991)
Prostate	Spain	Patients	—	S[b]	(Picurelli et al., 1991)
	Spain	Controls	—		(Picurelli et al., 1991)
Prostate	Turkey	Patients	—	S[b]	(Likili et al., 1991)
	Turkey	Controls	—		(Likili et al., 1991)
Gastric	China	Patients	—	NS[a]	(Liu, 1991)
	China	Controls	0.80 ± 0.07		(Liu, 1991)
Digestive	China	Patients	—	S[b]	(Ma and Jiang, 1993)
	China	Controls	—		(Ma and Jiang, 1993)
Colorectal	India	With advanced cancer	0.15	S[b]	(Gupta et al., 1993)
	India	Controls	0.85		(Gupta et al., 1993)
Breast	Turkey	Patients	1.35 ± 0.29	S[b]	(Yücel et al., 1994)
	Turkey	Controls	0.48 ± 0.13		(Yücel et al., 1994)
Breast	India	With advanced breast cancer	0.15	S[b]	(Gupta et al., 1991)
	India	Controls	0.89		(Gupta et al., 1991)
Leukaemia	France	Patients	—	S[b]	(Malvy et al., 1993)
	France	Controls	—		(Malvy et al., 1993)
Hepatic	China	Patients	—	NS[a]	(Hsing et al., 1991)
	China	Controls	—		(Hsing et al., 1991)

[a]Not statistically significant than the control group.
[b]Statistically significant lower zinc levels in patients with cancer than in the control group.

from melanoma decreases when the zinc intake from foodstuffs is related to an additional mineral supplementation of this element.

Taking into account these results, a zinc supplementation trial in areas where inhabitants consume diets with a low content of this element could be necessary, as a preventive measure for protection against the development of carcinogenic processes.

4.1.2. Copper

Serum copper levels obtained from patients with different types of cancer were not significantly different than in healthy controls ($P > 0.05$) (Table 3).

It is known that cancer causes an irregularity based on the corporal and metabolic distribution of copper. In the different studies considered there is still controversy about the incidence of copper levels on the genesis and evolution of the cancerous pathology. Studies performed on animals and humans showed that in cancer diseases an increase in serum ceruloplasmin and copper levels is produced, together with a decrease in the copper body turnover, therefore, copper concentrations in liver and kidney are lower (Linder, 1988).

Table 6 shows the results obtained in similar studies carried out by others. In many of them a significant increase in copper levels was produced in patients with breast cancer (Yücel et al., 1994; Gupta et al., 1991), colorectal cancer (Gupta et al., 1993), gastric cancer (Liu, 1991), malignant cancer (Jia, 1991), brain tumor of the type of metastatic carcinoma (Yoshinda et al., 1993), and gynaecological cancer (Chan et al., 1993), with respect to the serum copper concentrations determined in healthy subjects. Nevertheless, no significant differences were observed by others in patients with larynx cancer (Durak et al., 1994), brain cancer of the meningioma and malignant glioma type (Yoshida et al., 1993), cervical cancer (Arumanayagam et al., 1993), breast cancer (Overvad et al., 1993) and cancer of the digestive tract (Ma and Jiang, 1993) as regards healthy controls. Moreover, in other assays copper levels

Table 6
Serum or plasma copper levels determined by other investigators in healthy subjects when compared with patients with cancer

Type of cancer	Country	Subjects	Zn (mg/l)	Significance	Reference
Breast cancer	USA	Patients	1.31 ± 0.37	NS[a]	(Overvad et al., 1993)
	USA	Healthy controls	1.26 ± 0.36		(Overvad et al., 1993)
Malignant cancer	China	Patients	1.27	S[b]	(Jia, 1991)
	China	Healthy controls	—		(Jia, 1991)
Breast cancer	USA	Patients	1.67	S[b]	(Gupta et al., 1991)
	USA	Healthy controls	0.99		(Gupta et al., 1991)
Gastric carcinoma	China	Patients	0.95 ± 0.13	S[b]	(Liu, 1991)
	China	Healthy controls	0.80 ± 0.07		(Liu, 1991)
Colorectal cancer	USA	Patients	1.66	S[b]	(Gupta et al., 1993)
	USA	Healthy controls	0.99		(Gupta et al., 1993)
Cervical carcinoma	Switzerland	Patients	—	NS[a]	(Arumanayagam et al., 1993)
	Switzerland	Healthy controls	—		(Arumanayagam et al., 1993)
Breast cancer	Turkey	Patients	2.28 ± 0.38	S[b]	(Yücel et al., 1994)
	Turkey	Healthy controls	0.94 ± 0.23		(Yücel et al., 1994)
Brain cancer	Japan	Patients with meningioma	1.27 ± 0.13	NS[a]	(Yoshida et al., 1993)
	Japan	Patients with metastatic carcinoma	1.58 ± 0.16	S[b]	(Yoshida et al., 1993)
	Japan	Patients with glioma	1.28 ± 0.10	NS[a]	(Yoshida et al., 1993)
	Japan	Healthy controls	0.98 ± 0.11	S[b]	(Yoshida et al., 1993)
Gynaecological cancer		Patients	—		(Chan et al., 1993)
		Healthy controls	—	S[b]	(Chan et al., 1993)

[a] Not statistically significant than the control group.
[b] Statistically significant higher copper levels in patients with cancer than in the control group.

in renal cells were lower in patients with renal cancer than in controls (Hardell et al., 1994). This fact has also been noticed in the present study in patients with haematological cancer (0.95 ± 0.41 mg/l) and gynaecological cancer (1.04 ± 0.35 mg/l) versus the control group (1.10 ± 0.32 mg/l) (Table 3).

Others did not find any significant difference of serum copper and Cu/Zn ratios among normal volunteers, patients with benign diseases and those with stage I or II cancer (Ma and Jiang, 1993). However, in the group of stage III and IV cancer patients, both values increased significantly. Considering that this increase in serum or plasma concentrations is probably established in the more advanced stages of the cancer disease (Ma and Jiang, 1993; Gupta et al., 1991, 1993; Arumanayagam et al., 1993) the fact that in the present study only serum copper concentrations in patients with digestive cancer were found to be not significantly higher (1.13 ± 0.30) than the control group could be due to the incipient phase of the cancerous pathology, the wide variety of cancers included in every group and/or the low number of patients considered.

No significant correlation was observed among the variables (serum copper and zinc concentrations) in the regression analysis performed on patients with cancer. This finding could be related with the fact that when cancer disease appears, the homeostatic control and, therefore, serum levels of both minerals are controlled in a different way; serum zinc levels decrease significantly and serum copper levels are not affected. Thus, the behaviour of both elements in the cancer disease is independent. The precise mechanisms responsible for the alterations in serum mineral levels are still unclear and require further evaluation in the future.

4.2. Patients with cardiomyopathy

4.2.1. Zinc

Serum zinc concentrations were significantly lower in patients with ischemic cardiomyopathy than in controls and patients with acute myocardial infarction ($P < 0.05$) (Table 4).

Epidemiological studies of control cases performed on humans indicated contradictory results as regard serum and plasma zinc levels in the different cardiovascular diseases. However, most studies showed a significant decrease of such concentrations in diseases of the type of chronic rheumatic heart disease (Govindaraju et al., 1993), ischemic heart disease in patients developing heart failure dilated cardiomyopathy (Oster, 1993). In an assay performed on workers from industrial centers in Slovakia, no significant differences between serum zinc levels in hypercholesterolemic (workers with higher probability of undergoing cardiovascular diseases) and the control group (workers with normal plasma cholesterol levels) was indicated (Magalova et al., 1994).

It is important to notice that the trace element concentration profile (copper, zinc, iron) is different in patients with dilated cardiomyopathy from those of other heart diseases such as myocardial infarction and coronary heart disease (Oster, 1993). This has also been indicated in our study with zinc concentrations significantly lower in patients with ischemic cardiomyopathy than in those with acute myocardial infarction. Other researchers point out that the decrease in plasma zinc levels in patients with congestive heart failure is due to an excretion of larger amounts to zinc in urine, which may eventually lead to zinc deficiency (Golik et al., 1993). Moreover, others also established that cardiovascular alterations seem to reduce zinc serum levels, although hypertension increases them (Lopez et al., 1991).

At the moment controversy exists about the mechanism by which zinc could act in the human organism and affect the atherogenic index in a stage prior to the appearance of cardiovascular disease. It seems that serum zinc levels are correlated with plasma cholesterol level. This fact is still not very clear because while some researchers established that serum zinc levels tended to be higher in the hypercholesterolemic group (Magalova et al., 1994), others found an opposite effect (Thuillier-Juteau et al., 1987) or even no correlation between both parameters (Tiber et al., 1986).

4.2.2. Copper

No significant differences were observed

between serum copper levels in patients with cardiomyopathy when compared to the control group (Table 4; $P > 0.05$).

Comparing the results obtained in this study with those determined by others we observed the existence of contradictory data. Magalova et al. (1994) found that copper serum was positively related with cumulative factors of cardiovascular disease. Moreover, serum copper levels in patients with dilated cardiomyopathy also increased with respect to controls (Oster, 1993). The copper concentration profile is different in patients with dilated cardiomyopathy from that of other heart diseases (Oster, 1993; Dementera et al., 1993). They found that the copper concentration in blood was considerably lower in patients developing heart failure in the early post-perfusion period than in those with an uncomplicated post-operative period.

In our study no significantly lower and higher serum copper concentration in patients that had undergone ischemic cardiomyopathy and acute myocardial infarction than in healthy controls was observed (Table 4). Concomitantly, such as others previously established (Oster, 1993; Dementera et al., 1993), it seems that serum copper levels in patients with cardiomyopathy depends on the type and stage of cardiovascular disease.

It is interesting to indicate that a deficient intake of copper in the diet, or a high zinc/copper ratio cause an increase in hypercholesterolemy and, consequently, in cardiovascular risk (Allen and Klevay, 1978; Aalbers and Houtman, 1985; Allen, 1993; Al-Othman et al., 1994). This copper deficiency has been related to cardiovascular defects in both laboratory animals (rats) and humans.

Consequently, and taking into account the results obtained, we consider that the use of serum or plasma zinc and copper levels as valid indicators for the diagnosis of cancer or heart diseases suggested by some investigators (Gupta et al., 1991, 1993; Likili et al., 1991), must be considered as a possibility, although additional research must be carried out in the future. We have previously noted that a study of these correlations should include a specific type of cancer and cardiovascular disease, taking into account the advancing stage of the disease (Ma and Jiang, 1993; Yoshida et al., 1993; Magalova et al., 1994; Gupta et al., 1991, 1993; Arumanayagam et al., 1993; Govindaraju et al., 1993; Oster, 1993; Dementera et al., 1993). Both factors seem to have an influence on the distribution and metabolism of copper and zinc in the human organism.

References

Aalbers G, Houtman JPW. Relationships between trace elements and atherosclerosis. Sci Total Environ 1985;43:2.

Allen KGD, Klevay LM. Cholesterolemia and cardiovascular abnormalities in rats caused by copper deficiency. Atherosclerosis 1978;29:81–93.

Allen KG. Ischemic heart disease and dietary copper — towards a unifying hypothesis. Nutrition 1993;9:189–199.

Al-Othman AA, Rosenstein F, Ley KY. Pool size and concentration of plasma cholesterol are increased and tissue copper levels are reduced during early stages of copper deficiency in rats. J Nutr 1994;124:628–635.

Arnaud J, Faure H, Bourlard P, Denis B, Favier AE. Longitudinal changes in serum zinc concentration and distribution after acute myocardial infarction. Clin Chim Acta 1994;230:147–156.

Arumanayagam M, Wong FW, Rogers M, Swaminathan R. Serum ceruloplasmin plasma copper concentration and copper to ceruloplasmin ratio in cervical carcinoma. Gynecol Obstet Invest 1993;35:175–178.

Chan A, Wong F, Arumanayagam M. Serum ultrafiltrable copper, total copper and caeruloplasmin concentrations in gynaecological carcinomas. Ann Clin Biochem 1993;30:545–549.

Dementera II, Andrianova MIu, Dzemeshkevich SL, Iavarovskii AG, Lokslin LS. Changes in the content of microelements — copper, zinc and iron in the blood of patients following cardiopulmonary bypass. Anesteziol Reanimatol 1993;4:50–53.

Durak I, Kavutcu M, Canbolat O, Isik AU, Akyol O. Concentrations of some major and minor elements in larynx tissues with and without cancer. Biometals 1994;7:45–48.

Golik A, Cohen N, Ramot Y et al. Type II diabetes mellitus congestive heart failure, and zinc metabolism. Biol Trace Elem Res 1993;39:171–175.

Gupta SK, Shukla VK, Vaidya MP, Roy SK, Gupta S. Serum trace elements Cu/Zn ratio in breast patients. J Surg Oncol 1991;46:178–181.

Gupta SK, Shukla VK, Vaidya MP, Roy SK, Gupta S. Serum and tissue trace elements in colorectal cancer. J Surg Oncol 1993;52:172–175.

Govindaraju V, Prabhudev N, Gurappa M, Jawali VS, Chandrasekhara PM, Manjunath CN. Zinc in rheumatic heart valves. J Assoc Physic India 1993;41:653–654.

Hardell L, Wing AM, Ljunberg B, Oreifaldt AC, Degerman A, Halmans G. Levels of cadmium, zinc and copper in renal

cell carcinoma and normal kidney. Eur J Cancer Prev 1994;45:45–48.

Hsing AW, Guo W, Chen J et al. Correlates of liver cancer mortality in China. Int J Epidemiol 1991;20:54–59.

Jia ZG. Analysis of serum levels of selenium, zinc, and copper in 132 patients with malignant tumors. Chung Hua Yu Fang I Hsueh Tsa Chich 1991;25:205–207.

Johnson MA, Fischer JG. Is copper an antioxidant nutrient?. Rev Food Sci Nutr 1992;32:1–31.

Johnson PE, Milne DB, Lykken GL. Effects of age and sex on copper absorption, biological half-life, and status in humans. Am J Clin Nutr 1992;56:917–925.

Linder MC. Nutrición y metabolismo de los elementos traza. In: Linder MC, editor. Nutrición: Aspectos Bioquímicos, Metabólicos y Clínicos. Pamplona: Eunsa, 1988.

King JC, Keen CL. Zinc, 8th ed. In: Shils ME, Olson JA, Shike M, editors. Modern Nutrition in Health and Disease. Philadelphia: Lea and Febiger 1994:214–230.

Kirpatrick CS, White E, Lee JA. Case-control study of malignant melanoma in Washington State. II. Diet, alcohol, and obesity. Am J Epidemiol 1994;139:869–880.

Klevay LM, Moore RJ. Beer mitigates some effects of copper deficiency in rats. Am J Clin Nutr 1990;51:869–872.

Likili M, Ergen A, Celebi I. Zinc plasma levels in prostatic carcinoma and BDH. Int Urol Nephrol 1991;23:151–154.

Liu XG. Serum and tissue copper, zinc and selenium levels in patients with gastric carcinoma. Chung Hua Chung Liu Tsa Chih 1991;13:93–96.

Lopez C, Ocon DC, Mango MS, Frasquet I, De-Armino VA. Study of zinc and copper serum levels in dislipemias. Therapie 1991;46:17–20.

Ma EL, Jiang ZM. Ion-exchange chromatography in simultaneous determination of serum, copper and zinc levels in patients with cancer of digestive tract. Chim Med J Engl 1993;106:118–121.

Magalova T, Batkova A, Bederova A, Kajaba I, Puchonova I. Serum copper and zinc in industrial centers in Slovakia. Biol Trace Elem Res 1994;40:225–235.

Malvy DJ, Burtschy B, Arnaud J et al. Serum beta-carotene and antioxidant micronutrients in children with cancer, The 'Cancer in children and antioxidant micronutrients' French study group. Inst J Epidemiol 1993;22:761–771.

Martín-Lagos F, Navarro-Alarcón M, Terrés-Martos C, López-G de la Serrana H, López-Martínez MC. Serum zinc levels in healthy subjects from southeastern Spain. Biol Trace Elem Res, 1997 (In press).

McGrath LT, Douglas AF, McClean E et al. Oxidative stress and erythrocyte membrane fluidity in patients undergoing regular dialysis. Clin Chim Acta 1995;235:179–188.

Oster O. Trace element concentrations (Cu, Zn, Fe) in serum from patients with dilater cardiomyopathy. Clin Chim Acta 1993;214:209–218.

Overvad K, Wang DY, Olsen J et al. Copper in human mammary carcinogenesis: a case-cohort study. Am J Epidemiol 1993;137:409–414.

Picurelli L, Olcina PV, Roig MD, Ferrer J. Determination of Fe, Mg, Cu and Zn in normal and pathological prostatic tissue. Acta Urol Esp 1991;15:344–350.

Szymanska JA, Swietlicka EA, Piotrowski JK. Protective effect of zinc in the hepatotoxicity of bromobenzene and acetaminophen. Toxicology 1991;66:81–91.

Terrés-Martos C, Navarro-Alarcón M, Martín-Lagos F, López-G de la Serrana H, López-Martínez MC. Determination of copper levels in serum of healthy subjects by atomic absorption spectrometry. Sci Total Environ 1997;198:97–103.

Thuillier-Juteau Y, Jaudon MC, Clavel JP, Delattre J, Galli A. Serum zinc and copper in hypercholesterolemia. Pathol Biol 1987;35:387.

Tiber AM, Sakkai M, Joffe D, Ratnaparkhi MV. Relative value of plasma copper, zinc, lipids and lipoproteins as markers for coronary artery disease. Atherosclerosis 1986;62:105.

Williams CM, Dickerson JWT. Nutrition and cancer — some biochemical mechanisms. Nutr Res Rev 1990;3:75–100.

Wright AJA, Southon S, Bailey AL, Finglas PM. Nutrient intake and biochemical status of non-institutionalized elderly subjects in Norwich: comparison with younger adults and adolescents from the same general community. Br J Nutr 1995;74:453–475.

Yoshida D, Ikeda Y, Nakazawa S. Quantitative analysis of copper, zinc and copper/zinc ratio in selected human brain tumors. J Neurooncol 1993;16:109–115.

Yücel I, Arpaci F, Ozet A et al. Serum copper and zinc levels and copper/zinc ratio in patients with breast cancer. Biol Trace Elem Res 1994;40:31–38.