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Effects of selenium and zinc supplementation on nutritional status in patients with cancer of digestive tract†

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Objective: To evaluate the effect of oral administration of selenium and zinc tablets in patients with cancer of the digestive tract during chemotherapy.
Design: A case–control, randomized study.
Setting: Medical Oncology, II University of Naples, Naples, Italy.
Subjects: A total of 60 patients (median age 55 y, range 46–61 y) with diagnosis of gut cancer were randomized in 1999. Patients were treated for 60 days with chemotherapy.
Interventions: Trace elements were measured by atomic absorption spectroscopy. The nutritional status of the patients was assessed by biochemical and bio-impedance analysis (BIA) parameters in basal condition and after 60 days of treatment. Oral administration of selenium and zinc in oral tablet form for 50 days was Se 200 μg/day (50 μg/tablet) and Zn 21 mg/day (7 mg/tablet).
Results: Both in the basal condition and at 60 days all patients were malnourished. Selenium and zinc concentrations were significantly lower ($P < 0.01$) whereas copper concentration was significantly higher ($P < 0.01$) in cancer patients than in control subjects. However, 21/30 (70%) of those treated with Se and Zn did not showed a further worsening of nutritional status and experienced a significant decrease of asthenia with an increase of appetite. On the other hand, 24/30 (80%) untreated patients had a significant decline of all parameters studied after 60 days (prealbumin, cholesterol, transferrin, $P < 0.05$ *vs* 0 time; total proteins, albumin/globulin ratio, $P < 0.01$ *vs* 0 time; fat-free mass, fat mass, Na^+/K^+ ratio, body mass index $P < 0.05$ *vs* 0 time; fat free mass/fat mass, total body water, extra cellular/intra cellular water, basal metabolic rate: $P < 0.01$ *vs* 0 time).
Conclusions: Data indicate that Se and Zn supplementation may improve the clinical course of general conditions in patients with gut cancer. These effects of Se and Zn require confirmation in an independent trial of appropriate design before new public health recommendations regarding Se and Zn supplementation can be made.
Descriptors: selenium; zinc; supplementation; digestive tract cancer
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Introduction

Trace elements consist mostly of metal ions mainly acting as basic components of essential enzymatic systems or proteins, which play major roles in the physiology of the gastrointestinal tract (Jackson, 1989). The relationship between trace elements and cancer development is not completely clear. Decrease in magnesium, zinc and selenium serum concentration has been described as associated with carcinogenesis in man (Underwood, 1977; Burk, 1986; Key, 1994). Also, selenium has been demonstrated to be cancer protective, at least in animal models (Nelson *et al*, 1996). A significant decrease in selenium and zinc serum levels, as well as increase in copper serum concentration, has been shown in cancer patients (Burk, 1986; Gibson, 1994; Ma & Jiang, 1993; Shenberg *et al*, 1995). The relationship between these alterations and the disease course (Block, 1993) and/or the nutritional status of cancer patients has been investigated (Diplock, 1993). These studies suggest that trace elements serve as co-factors in several metabolic pathways and a decrease in their concentration may facilitate the malnutrition process that takes place in cancer patients. Moreover, in patients with cancer of digestive tract, serum zinc/copper ratio decreases progressively mainly at stages III and IV, while

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no statistically significant change has been noted in patients with benign tumours of digestive tract at stage I and II (Ma & Jiang, 1993).

Chemotherapy has been found to be associated with alteration of serum concentration of a number of trace elements (Pezonaga *et al*, 1996). This has been related to organic immunodepression caused by cytostatics, which in turn may lead to impairment of the nutritional status. However, whether chemotherapy-induced alteration of trace element serum concentration is due to a direct effect of the drugs or is rather contributed to by chemotherapy-related malnutrition is not clear.

From this, it is evident that the cancer patient needs supplementation with the defective trace elements. These, in fact, can diminish the damage induced by peroxidation (StAahelin, 1993).

Many studies have confirmed the effect of supplementation with oligoelements in cancer development and progression. Rao *et al* suggest a potential modest benefit for short-term intervention with multiple vitamins and minerals on squamous epithelial cell proliferation of the oesophagus in high-risk population (Rao *et al*, 1994).

Our study was designed to evaluate the effect of oral administration of selenium and zinc tablets on patients with malignancies of the gastrointestinal tract during chemotherapy. Also, we evaluated whether any change in trace element serum levels correlated with the nutritional status of the patients.

Patients and methods

After informed consent and approval of the Ethical Committee of our department we studied 60 patients with cancer of digestive tract: 28 with colorectal carcinoma (M/F 16/12; median age 57 y, range 53–61 y), 20 with gastric adenocarcinoma (M/F 12/8; median age 56 y, range 53–61 y), and 12 with oesophageal carcinoma (M/F 9/3; median age 54 y, range 46–59 y).

Patients did not have any other major disease nor had they been treated with antineoplastic drugs or radiotherapy. We also studied 30 healthy subjects, matched for age and sex, in order to have a baseline value for trace element serum levels and for nutritional status. Patients and controls were HIV-negative, non-smokers, non-drinkers. In particular, we accurately excluded from the study patients with past or present alcohol abuse, to eliminate the possible interference of ethanol on levels of trace elements and on the other parameters studied.

The nutritional status of each patient was assessed through a combination of serum and bio-impedance parameters (BIA Akern 109S) before and at the end of the treatment. The BIA Akern 109S calculates the reactance and the resistance of the human body; the computer program analysed weight, height, reactance and resistance and it calculated the parameters of nutritional status.

Serum selenium, zinc and copper were measured before and after therapy (60 days).

All of the patients were treated for 2 months at 14 day intervals with metotrexate (MTX) 500 mg/m^2 intravenously on the first day, 5-fluorouracil (5FU) 250 mg/m^2 intravenously on the second day and L-Folinic Acid (LFA) 600 mg/m^2 intravenously on the second day.

In half of these patients Se and Zn in oral tablet form was administered for 50 days: Se 200 μg/day (50 μ/tablet) and Zn 21 mg/day (7 mg/tablet) (Solgar Vitamins House, Chiltern Commerce CTR, Chesham, London).

Trace elements were measured by atomic absorption spectroscopy. In particular, for selenium measurement, we used a model 4100 atomic absorption spectrophotometer with Zeeman background corrector, a model HGA (heated graphite atomiser), an AS-70 auto sampler, a model DEC pc 316 Sx data station, and an electrodeless discharge lamp for Se (all from Perkin-Elmer Corporation). Pyrocoated graphite tubes and pyrolitic graphite VoV platforms were from Perkin-Elmer. Doubly distilled water was used for all reagents and standard solutions. The matrix modifiers were 0.06 g Pd and 0.01 g $Mg(NO_3)_2$ per 100 ml. We diluted the serum samples and the calibrating standard materials two fold with aqueous solution of Triton X-100 (BDH Chemicals). We then injected into the furnace 20 μl of the diluted solution, followed by 5 μl of the matrix-modifier solution (Bindoli *et al*, 1986; Minoia & Cavalleri, 1983; Burrini *et al*, 1993; Morisi *et al*, 1988).

For atomic absorption measurement of zinc and copper we used a model 3030 flame atomic absorption spectrophotometer (FAAS), an AS-50 auto sampler, an electrodeless discharge lamp (for Zn or for Cu), and model EPSON LX 400 data printer (all from Perkin-Elmer Corporation). Working standard solutions were prepared from a stock standard solution of copper or zinc (Carlo Erba). We diluted the serum samples and the calibrating standard materials two-fold (for copper) and five-fold (for zinc) with distilled water (Dello Russo *et al*, 1986).

Significance of differences was assessed by Student's *t*-test. Differences were considered to be significant if $P < 0.05$.

Results

At time 0 most patients showed a significant alteration of the nutritional parameters compared with controls (Tables

Table 1 Biochemical parameters of nutritional status in 30 cancer patients who were given Se and Zn (before and after 60 days of chemotherapy) and in 30 control subjects (mean ± s.d.)

	0 days *A*	*60 days* *B*	*Controls* *C*
Prealbumin (mg/dl)	23.2 ± 4.2*	23.8 ± 7.3	27.8 ± 5.3
Cholinesterase (U/L)	7243 ± 2830*	8240 ± 2620	9764 ± 3461
Cholesterol (mg/dl)	144.5 ± 62.5**	134.4 ± 98.4	180.8 ± 43
Transferrin (mg/dl)	288.4 ± 90.4**	274.8 ± 92.2	339.5 ± 84.9
Total proteins (g/dl)	5.6 ± 1.2†	5.4 ± 1.3	7.4 ± 1.2
Albumin/globulin ratio	1.06 ± 0.11†	1.02 ± 0.13	1.52 ± 0.12

A *vs* C *$P < 0.01$; A *vs* C **$P < 0.05$; A *vs* C †$P < 0.001$.

Table 2 Biochemical parameters of nutritional status in 30 cancer patients who were not given Se and Zn (before and after 60 days of chemotherapy) and in 30 control subjects (mean ± s.d.)

	0 days *A*	*60 days* *B*	*Controls* *C*
Prealbumin (mg/dl)	$23.9\pm2.9^{*}$	$20.7\pm2.2^{**}$	27.8 ± 5.3
Cholinesterase (U/L)	$7295\pm2632^{*}$	6841 ± 2235	9764 ± 3461
Cholesterol (mg/dl)	$143.8\pm48.5^{\dagger}$	$121.5\pm35.8^{**}$	180.8 ± 43
Transferrin (mg/dl)	$297.5\pm76.3^{\dagger}$	$253.7\pm61.5^{**}$	339.5 ± 84.9
Total proteins (g/dl)	$5.9\pm1.3^{\dagger}$	$5.1\pm0.9^{\S}$	7.4 ± 1.2
Albumin/globulin ratio	$1.13\pm0.24^{\dagger}$	$1.01\pm0.13^{\S}$	1.52 ± 0.12

A *vs* C $^{*}P<0.01$; A *vs* C $^{\dagger}P<0.05$; A *vs* C $^{\ddagger}P<0.001$; B *vs* A $^{**}P<0.05$; B *vs* A $^{\S}P<0.001$.

Table 3 BIA parameters of nutritional status in 30 cancer patients who were given Se and Zn (before and after 60 days of chemotherapy) and in 30 control subjects (mean ± s.d.)

	0 days *A*	*60 days* *B*	*Control* *C*
%FFM	$77.6\pm6.4^{*}$	78.5 ± 6.5	71.5 ± 7.1
%FM	$21.8\pm6.5^{*}$	22.7 ± 7.2	27.9 ± 8.1
FFM/FM	$3.55\pm0.9^{**}$	2.83 ± 1.2	2.56 ± 0.9
%BTW	$59.4\pm5.1^{**}$	59.0 ± 4.82	51.4 ± 7.1
ECW/ICW	$0.99\pm0.13^{**}$	1.02 ± 0.14	0.95 ± 0.1
Na^+/K^+ ratio	$1.06\pm0.2^{\dagger}$	1.08 ± 0.23	0.93 ± 0.23
BMI	$23.7\pm3.8^{\dagger}$	22.9 ± 3.5	26.2 ± 4.1
BMR (kcal)	$1448\pm162^{**}$	1431 ± 161	2530 ± 202
Ph A (grade)	5.9 ± 0.7	5.6 ± 0.8	5.7 ± 1.1

A *vs* C $^{*}P<0.001$; A *vs* C $^{\dagger}P<0.05$; A *vs* C $^{\ddagger}P<0.01$.
%FFM = percentage fat-free mass; %FM = percentage fat mass; %BTW = percentage total body water; ECW = extracellular water; ICW = intracellular water; BMI = body mass index; BMR = basal metabolic rate; Ph A = phase angle.

Table 4 BIA parameters of nutritional status in 30 cancer patients who were not given Se and Zn (before and after 60 days of chemotherapy) and in 30 control subjects (mean ± s.d.)

	0 days *A*	*60 days* *B*	*Control* *C*
%FFM	$75.5\pm4.3^{*}$	$79.6\pm5.4^{\ddagger}$	71.5 ± 7.1
%FM	$22.7\pm4.7^{*}$	$20.3\pm6.2^{\ddagger}$	27.9 ± 8.1
FFM/FM	$3.12\pm1.2^{**}$	$3.68\pm1.4^{\S}$	2.56 ± 0.9
%BTW	$58.3\pm6.2^{**}$	$60.2\pm3.7^{\S}$	51.4 ± 7.1
ECW/ICW	$0.99\pm0.13^{**}$	$1.07\pm0.09^{\S}$	0.95 ± 0.1
Na^+/K^+ ratio	$1.04\pm0.3^{\ddagger}$	$1.09\pm0.19^{\ddagger}$	0.93 ± 0.23
BMI	$23.9\pm3.5^{\dagger}$	$21.4\pm2.6^{\ddagger}$	26.2 ± 4.1
BMR (kcal)	$1672\pm185^{*}$	$1289\pm153^{\S}$	2530 ± 202
Ph A (grade)	5.8 ± 0.9	5.8 ± 0.7	5.7 ± 1.1

A *vs* C $^{*}P<0.001$; A *vs* C $^{\dagger}P<0.05$; A *vs* C $^{*}P<0.01$; B *vs* A $^{\ddagger}P<0.05$; B *vs* A $^{\S}P<0.01$.
%FFM = percentage fat-free mass; %FM = percentage fat mass, %BTW = percentage body total water; ECW = extracellular water; ICW = intracellular water; BMI = body mass index; BMR = basal metabolic rate; Ph A = phase angle.

1–4). The diagnosis of malnutrition was based on anthropometrical and clinical findings (presence of oedema, loss of subcutaneous tissue and reduced muscle mass). At 60 days the above-mentioned parameters were more altered in the patients that had not followed the support therapy; in fact, 21 of 30 patients (70%) that had taken Se and Zn did not show a further decline of nutritional status compared to day 0. Instead, 24 of 30 (80%) patients in the other group showed a further worsening of their general condition (prealbumin, cholesterol, transferrin, $P<0.05$ *vs* 0 time; total proteins, albumin/globulin ratio, $P<0.01$ *vs* 0 time; fat-free mass (% FFM), fat mass (%FM), Na^+/K^+ ratio, body mass index (BMI), $P<0.05$ *vs* 0 time; FFM/FM, total body water (%BTW), extracellular/intracellular water (ECW/ICW), basal metabolic rate (BMR), $P<0.01$ *vs* 0 time). At the anamnesis, furthermore, 70% (21/30) of the patients treated reported a decrease in asthenia and an increase in appetite. Tables 5 and 6 show zinc, selenium and copper serum concentrations in healthy volunteers and in cancer patients (treated and untreated) before and after chemotherapy: at the end of therapy, selenium and zinc serum levels showed a significant increase in patients treated and a decrease in untreated patients compared with baseline values. Copper concentration at the end of the therapy decreased in treated patients and increased in untreated patients compared with baseline concentration. Plasma C-reactive protein levels measured before and after chemotherapy resulted in a normal range (< 0.5 mg/dl).

Discussion

Trace elements play a major role in the regulation of several functions in the gut (Jackson, 1989). A reduction in the serum levels of trace elements has been described in

Table 5 Serum levels of trace elements in 30 cancer patients who were given Se and Zn (before and after 60 days of chemotherapy) and in 30 control subjects (mean ± s.d.)

	0 days *A*	*60 days* *B*	*Control* *C*
Selenium (μg/dl)	$55.7\pm7.3^{*}$	$62.4\pm9.3^{\dagger}$	65.0 ± 12.0
Zinc (μg/dl)	$78.9\pm7.8^{*}$	$84.2\pm5.4^{\S}$	87.5 ± 9.70
Copper (μg/dl)	$110.9\pm16^{*}$	$101.1\pm12.8^{\dagger}$	95.5 ± 13.2

$^{*}P<0.01$ A *vs* C; $^{\dagger}P<0.05$ B *vs* A; $^{\S}P<0.02$ B *vs* A.

Table 6 Serum levels of trace elements in 30 cancer patients who were not given Se and Zn (before and after 60 days of chemotherapy) and in 30 control subjects (mean ± s.d.)

	0 days A	*60 days B*	*Control C*
Selenium (μg/dl)	$56.4\pm8.4^{*}$	$51.4\pm7.2^{**\dagger}$	65.0 ± 12.0
Zinc (μg/dl)	$79.5\pm8.6^{*}$	$73.4\pm7.4^{\dagger\S}$	87.5 ± 9.70
Copper (μg/dl)	$111.9\pm19^{*}$	$118.4\pm11^{\dagger}$	95.5 ± 13.2

$^{*}P<0.01$ A *vs* C; $^{**}P<0.05$ B *vs* A; $^{\dagger}P<0.001$ B *vs* C; $^{\S}P<0.02$ B *vs* A.

a number of gastrointestinal diseases such as Crohn's disease as a consequence of altered absorption (Ringstad *et al*, 1993; Animashaun *et al*, 1990) and in viral cirrhosis as a consequence of altered metabolism and poor intake (Loguercio *et al*, 1997). Trace element serum concentration is also influenced by the nutritional status of patients and by the stage of a given disease (Underwood, 1977; Hambidge, 1987). A decrease in the serum concentration of selenium and zinc as well as an increase in serum levels of copper has also been described in cancer (Ma & Jiang, 1993; Shenberg *et al*, 1995).

The effects of chemotherapy on the metabolism of essential trace elements has been studied (Pezonaga *et al*, 1996). Cisplatin treatment has been shown to cause a significant decrease in the serum concentrations of Cu, Zn and Mg whereas Se serum levels remained unchanged (Pezonaga *et al*, 1996).

Polychemotherapy may alter the nutritional status of patients directly or indirectly (Douglas, 1997) by causing nausea, vomiting, anorexia and ulceration of the oral mucosa. Moreover, drugs that affect cell proliferation such as thioguanine, methotrexathe, fluorouracil, vinca's alkaloid, actinomycin D, hydroxyurea and daunomycin, may cause malabsorption (Trier, 1962a,b). It has been hypothesized that the effect on trace elements is the consequence of the alteration of the nutritional status induced by chemotherapy (Iodice *et al*, 1997).

Our study confirms that the serum levels of selenium, zinc and copper are altered in the neoplastic patients. In particular selenium and zinc serum levels are decreased whereas copper serum levels are increased. Zinc is a negative acute phase reactant (Melichar *et al*, 1994; Craig *et al*, 1990) and the copper concentrations increase as part of the inflammatory response (Sattar *et al*, 1997a; Shenkin, 1995). More recently selenium has also been described as acting as a negative acute phase reactant (Sattar *et al*, 1997b). Therefore, the changes in trace element concentrations seen in cancer patients (a model of chronic inflammation) relative to controls, could simply be the result of inflammation. To address this issue we measured C-reactive protein plasma levels in controls and in neoplastic patients before and after chemotherapy. We found comparable C protein plasma levels in controls and in neoplastic patients. Moreover, C protein plasma levels are not altered by chemotherapy, thus making it unlikely that the change in trace element concentrations is the reflection of the underlying process.

The decrease of trace elements in neoplastic patients may have various metabolic and clinical implications. Selenium deficiency may interfere with free-radical mediated damage and may be associated with the progression of cancer. Also, the decrease of zinc potentiates the toxicity of other metals, such as iron and copper. Moreover, zinc regulates the function of cytochromes (Loguercio *et al*, 1997), stabilizes plasma membranes and SH groups (Block, 1993), reduces lipid peroxidation (Faber *et al*, 1995), influences the deposition of hepatic collagen and the activity of the prolyl-hydroxylase (Loguercio *et al*, 1997), affects the urea synthesis capability and therefore the ammonia detoxification (Faber *et al*, 1995) and maintains the normal plasma values of vitamin A (StAahelin, 1993). Chemotherapy and radiation increase the requirements for antioxidant compounds. Supplementation can diminish the damage induced by peroxidation.

Our data confirm the presence of the alteration of the nutritional status at the moment of the first diagnosis of cancer. In addition, the utility of the support therapy with selenium and zinc has emerged: these, in fact, intervening like enzymatic cofactors in many metabolic processes of synthesis are efficacious in decreasing and/or in delaying the inevitable cachexy. The consequent immune system depression influences the evolution of the neoplastic disease and the chance of success of the chemotherapeutic treatment, with consequent alteration of the quality of life of the cancer patient.

Since trace elements are relevant to homeostasis in several organ systems, we suggest monitoring and correcting trace element serum concentration prior to and during administration of antineoplastic drugs.

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