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Selenium, Zinc, Iron and Copper Levels in Serum of Patients with Arterial and Venous Leg Ulcers

MAGNUS S. ÅGREN, HANS-ERIC STRÖMBERG, ANDERS RINDBY and GÖRAN HALLMANS

Clinic I, Vasa Hospital, Department of Physics, Chalmers University of Technology, Gothenburg, and Departments of Nutritional Research and Pathology, University of Umeå, Umeå, Sweden

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The total serum concentrations of selenium, zinc, iron and copper were determined in geriatric patients with and without leg ulcers. The levels of selenium, zinc and iron were significantly lower and the copper/zinc ratio was significantly higher in the leg ulcer group compared with control patients. The serum-copper level and the serum-copper/zinc ratio were raised in patients with poor ulcer healing. *Key words: Trace elements; Wound healing; Diabetes mellitus; Albumin.* (Received November 7, 1985.)

H.-E. Strömberg, Clinic I, Vasa Hospital, S-411 33 Gothenburg, Sweden.

The main causes of leg ulcers are in most cases vascular disturbances. Primary treatment should aim at eliminating these. However, secondary concomitant systemic and local factors might also be involved in the pathogenesis and/or aggravate the condition.

Ulceration of the skin in the lower legs is often associated with low serum-zinc levels (1, 2). Oral zinc therapy is believed to restore the healing capacity in these patients (2, 3) although this finding has not been reproduced in all clinical trials (4, 5). Other trace elements such as iron and copper are involved in biochemical reactions during wound healing (6). Selenium is associated with the enzyme glutathione peroxidase (7). Glutathione peroxidase has antioxidant activity and may prevent tissue damage. In conjunction with a clinical trial (8) we have compared the serum concentrations of selenium in addition to zinc, iron and copper in leg ulcer patients with the values measured in control patients.

PATIENTS

Twenty-four patients (16 women) aged 81±6 (mean±SD) years with an initial ulcerated area of 5.1±5.0 cm^2 were studied. Of these, eight had well-controlled type II diabetes mellitus (3.4±4.0 cm^2), all eight were treated with sulphonylureas. Twelve of the patients (five diabetics) had arterial (3.9±3.1 cm^2) and twelve (three diabetics) venous (6.5±6.4 cm^2) ulceration. Diagnosis of ulcer type was made from clinical signs and using the Doppler technique (8). Patients whose symptoms clearly indicated more than one cause for the ulceration were excluded. Forty patients (21 women) aged 80±5 years with dementia but without ulcers and no leg ulcer history served as a homogeneous control group, comparable in terms of age, calendar time and care. Patients with concomitant diseases known to alter serum trace element levels, i.e. infectious diseases, rheumatoid arthritis, major liver and kidney disorders, malignancies, and recent myocardial infarction, were excluded. The patients were given an ordinary, nutritionally adequate hospital diet. No patients received corticosteroids, zinc, iron, copper or selenium systemically.

METHODS

Venous blood samples were taken without stasis in the morning after overnight fasting. Haemolysed samples were discarded. All glassware was washed with acid and rinsed in deionized water. Serum was analysed on selenium, iron, copper and zinc using the energy dispersive X-ray fluoresence (XRF)

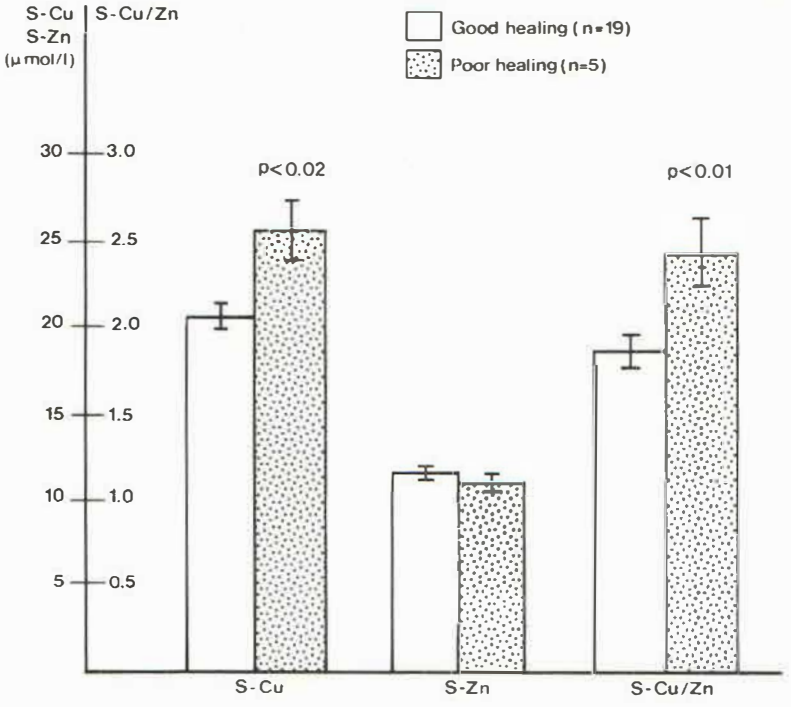

Fig. 1. Serum-copper (S-Cu), serum-zinc (S-Zn) and serum-copper/zinc ratio (S-Cu/Zn) presented as the mean values ± SEM in relation to healing in leg ulcer patients (XRF). S-Cu and S-Cu/Zn were significantly increased in patients with poor healing.

method (9) enabling simultaneous multielement analysis. The serum concentrations of copper and zinc were also measured in the leg ulcer group using atomic-absorption spectrophotometry (AAS) (10). Parallel measurements of the serum-copper ($n=33$) and serum-zinc concentration ($n=33$) performed with AAS and XRF yielded correlation coefficients of $r=0.92$ and $r=0.78$, respectively. The albumin serum concentration was determined by a photometrical standard method.

Healing was assessed as "good" if: (A) visible granulations appeared in the ulcer, or if there were visible granulations present before treatment, the initial ulcer area was reduced by at least 25% in the case of arterial and 50% in the case of the venous ulcers; and (B) the ulcer was free from slough over a period of 8 weeks. Healing was assessed as "poor" if an enlargement of the initial ulcer area exceeding 50% occurred, antibiotics were required, or criteria (A) and (B) were not fulfilled within 8 weeks (8).

Correlation coefficients (r) were calculated. Results were subjected to the t-test for unpaired observations. Differences were considered significant if the p-value<0.05.

RESULTS

Leg ulcer patients versus controls

The concentrations of selenium, zinc and iron were significantly lower and the copper/zinc ratio was significantly increased in the leg ulcer group (Table I). The mean serum albumin value was within the normal range in the leg ulcer patients and did not differ significantly from that of the control patients (Table I).

Subanalysis

Age and sex. No correlation was found between these two variables and the levels of examined trace elements in the two groups.

Albumin. Neither of the four elements were correlated with serum-albumin in the leg ulcer group or the control group.

Table I. *Results of serum analyses of leg ulcer patients and controls*

Reference values for iron (Fe), copper (Cu), zinc (Zn) and selenium (Se) for healthy adults are included for comparison

Serum level	Leg ulcer patients[a] (n=24)	Controls[a] (n=40)	p	Healthy adults[b] (mean and no. of obs. in parenthesis)
Albumin (g/l)[c]	36.0±4.5	33.8±3.2	NS	
Fe (μmol/l)	19.7±7.2	26.9±16.1	<0.05	19.5 (2662)
Cu (μmol/l)	22.0±3.1	23.6±6.3	NS	18.7 (2182)
Zn (μmol/l)	11.0±1.2	16.8±7.6	<0.001	17.6 (1961)
Cu/Zn ratio	1.97±0.42	1.47±0.49	<0.001	
Se (μmol/l)	1.01±0.51	1.27±0.51	<0.05	1.54 (507)

[a] Mean ± SD. Fe, Cu, Zn and Se levels were determined with XRF.
[b] Pooled values obtained from several different investigations using different analytical methods (11).
[c] Normal range: 36–50 g/l.

Ulcer type. No significant differences were recorded with respect to etiology and the serum concentrations of iron, copper, zinc or selenium.

Healing. The serum-copper level and serum-copper/zinc ratio were significantly increased in the five patients showing impaired healing, measured both with XRF and AAS (Fig. 1). No intergroup differences were detected regarding the serum levels of zinc, iron or selenium and healing. The serum-albumin figures did not differ significantly; 36.8±5.7 g/l for the patient with poor healing and 35.8±4.3 g/l for the patients with good healing.

Diabetes. The mean serum-copper value was significantly (p<0.05) higher in the diabetic patients (diabetics: 23.8±5.0 μmol/l; non-diabetics: 20.3±3.0 μmol/l). The difference did not reach significance when measured with AAS. The mean serum-albumin value was 34.5±5.2 g/l for the diabetic group and 36.9±4.0 g/l for the non-diabetic group; a non-significant difference. Six of the eight diabetic patients healed well and showed a similar healing ability to that of the non-diabetic patients.

DISCUSSION

Trace elements such as selenium, zinc, iron and copper are needed in sufficient amounts for intact immunological and inflammatory reactions (12). Deficiencies of these elements might therefore contribute to the cause and/or the course of the ulceration of the skin. Our findings indicate that selenium, zinc and iron are reduced in serum in leg ulcer patients.

In serum, trace elements are usually bound to proteins. However, small amounts can exist in unbound or "free" form. The principal transport protein for iron is transferrin, and for copper it is ceruloplasmin and albumin. About 30–40% of zinc is tightly bound to α_2-macroglobulin and about 50–60% is loosely bound to albumin; although we did not detect any correlation between serum-albumin and zinc in our patients. The chief selenium serum binders are not completely identified. In this investigation the total concentrations of the elements, i.e. both the bound and free forms, were measured.

The serum-copper level and the serum-copper/zinc ratio were raised in patients showing impaired healing but no difference was seen in serum-zinc concentration compared with patients with adequate healing (cf. Fig. 1). Poor healing was not attributed to hypoalbuminemia (6) since the serum-albumin levels were similar irrespective of healing result. This indicates that the serum-copper concentration and/or the serum-copper/zinc ratio might be of more prognostic value than serum-zinc in predicting the course of healing. One

explanation could be that the increased serum-copper level was due to a more pronounced local chronic inflammatory state because of the proposed relationship between the serum-copper level and inflammatory conditions (13). Comparison of serum-copper levels in patients with non-healed and healed ulcers could be one procedure to test the hypothesis.

Patients with non-insulin dependent diabetes mellitus had a higher serum-copper concentration. This finding was most probably related to increased levels of circulating ceruloplasmin since the ceruloplasmin level is elevated in diabetes (14).

Selenium deficiency may theoretically delay wound healing by impairing the local blood supply through an inhibited prostacyclin synthesis (7). DNA and RNA-polymerases, enzymes linked with cellular proliferation and protein synthesis, are zinc dependent (6). Iron is essential for the enzymatic hydroxylation reactions during collagen biosynthesis (6). However, it is impossible to conclude whether the low serum levels reflect actual deficiency states or merely a redistribution of the trace elements within the body. On the other hand, there is experimental evidence that the plasma concentration is an accurate measure of the body status in the case of zinc (15). The clinical and biochemical response after the administration of the element is often the most reliable way to diagnose a deficit (2, 5).

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