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Zinc Supplementation in Alcoholic Cirrhosis

A Double-Blind Clinical Trial

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ABSTRACT. A double-blind clinical trial with zinc sulfate, 0.2 g three times daily, and a placebo was performed in 30 patients with biopsy-proven alcoholic liver cirrhosis. The disease was in a stable phase, and none of the patients showed evidence of a decompensated liver function. Parameters of liver function, taste acuity, dark adaptation and of zinc and vitamin A metabolism were followed for six weeks. In the zinc-treated group of 16 patients, serum zinc rose from a normal mean value of 13.3 to 17.4 μmol/l, whereas the mean serum vitamin A level remained practically unaltered within the normal range, 1.89 at the entry and 1.83 μmol/l at the end of the study. Plasma prothrombin and serum alkaline phosphatase levels of the zinc group increased and serum bilirubin and serum carotene decreased significantly. The dark adaptation did not change, but the taste function was significantly improved during zinc treatment. The results indicate that zinc supplementation causes alleviation of certain abnormalities of cirrhotics, which deserves further attention.

Key words: alcoholic cirrhosis, alkaline phosphatase, dark adaptation, taste function, zinc sulfate therapy.

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It has long been known that patients with liver cirrhosis may show subnormal levels of zinc and vitamin A in plasma and liver, and, paradoxically, hyperzincuria (5, 10, 17, 18). In zinc deficient rats, low plasma zinc concentrations are also accompanied by low levels of vitamin A (14). As in cirrhotic man (13), the low plasma vitamin A levels of zinc deficient rats reflect low plasma concentrations of retinol-binding protein, which is produced by the liver (15). Following zinc therapy in zinc deficient rats, plasma vitamin A increases, whereas vitamin A supplementation has no such effect (14). The effect of zinc is attributed to a normalization of hepatic production of retinol-binding protein, which is needed for the transport of vitamin A and for its mobilization from liver stores (15).

Cirrhosis is often associated with night blindness (10) and colour blindness (2), which may be resistant to vitamin A therapy even in high doses. It has been suggested that such disorders are due to zinc deficiency (3). Vallee et al. (18) observed that the bromsulfalein retention test was improved in six cirrhotics who were given small oral doses of zinc. As controlled trials with zinc for cirrhosis have never been performed, the present investigation was undertaken with the purpose of studying the effects of oral zinc sulfate on parameters of liver function, as well as of dark adaptation, taste function and of vitamin A and zinc metabolism in patients suffering from alcoholic cirrhosis in a stable phase.

PATIENTS AND METHODS

Thirty-two outpatients with biopsy-proven alcoholic cirrhosis were initially included in a 6-week double-blind clinical trial with zinc sulfate and a placebo. The patients were randomly assigned either to a group receiving coated zinc sulfate tablets of 0.2 g (=45 mg zinc) or to a group receiving lactose tablets of identical appearance. The tablets and the code were provided by the Pharmacy Laboratory, Rigshospitalet. One tablet was to be taken three times daily after meals. The mean age of the females was 59 years (range 53–66) and of the males 56 years (range 30–73). All patients had a past history of alcoholism which had caused liver cirrhosis, but they now claimed to abstain from alcohol. Twenty-six (80%) of the patients had had bleeding from oesophageal varices (10 cases), encephalopathy (10 cases) or ascites (16 cases). Sixteen patients were receiving diuretics (thiazides, furosemide, thalidone) together with a potassium supplement (Kaleorid®) (14 cases) or with spironolactone (Aldactone®) (2 cases). Two patients took disulfiram (Antabus®). The individual medication was continued unaltered during the trial. The general health and the social condition of the patients were considered to be good, and the liver disease was in a stable phase. Two drop-outs were due to hospitalization at an-

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Table I. *Laboratory analyses and taste score values of alcoholic cirrhosis patients receiving oral zinc sulfate or placebo for 6 weeks*

Mean values with range in parentheses

	Reference limits	Zinc group ($n=16$)			Placebo group ($n=14$)		
		Entry	6 weeks	p^b	Entry	6 weeks	p^b
Hb (g/l)	113–169	145 (121–172)	143 (113–166)	>0.2	150 (113–171)	148 (118–174)	>0.6
Thrombocytes (10^9/l)	160–400	157 (37–262)	152 (52–260)	>0.3	166 (80–267)	167 (68–264)	>0.9
P-albumin (g/l)	35.4–54.1	34.5 (27.2–41.4)	34.0 (27.9–42.8)	=0.3	34.2 (26.0–43.2)	34.8 (25.7–41.7)	>0.5
P-IgG[a] (g/l)	6.62–15.7	12.5 (5.5–26.2)	12.7 (8.5–26.3)	>0.5	13.3 (7.9–20.7)	12.6 (7.3–19.6)	<0.05
P-IgA[a] (g/l)	0.56–3.30	3.42 (1.20–8.09)	3.28 (1.14–7.92)	>0.6	3.88 (2.44–7.87)	3.91 (2.30–7.24)	>0.8
P-prothrombin[a](arb. U)	0.57–1.43	0.85 (0.50–1.45)	0.94 (0.51–1.30)	<0.05	0.76 (0.54–1.16)	0.78 (0.54–1.32)	>0.5
S-bilirubin[a] (μmol/l)	2–17	12.9 (7–25)	10.1 (4–24)	<0.005	21.8 (9–87)	19.7 (9–105)	>0.4
S-alkaline phosphatase[a] (U/l)	50–275	270 (155–665)	304 (190–560)	<0.05	281 (200–500)	269 (205–400)	>0.4
S-alanine aminotransferase[a] (U/l)	10–40	26.2 (13–110)	28.1 (13–98)	>0.4	28.6 (20–57)	27.7 (17–63)	>0.4
S-magnesium (mmol/l)	0.78–1.03	0.76 (0.63–0.94)	0.78 (0.57–0.93)	>0.2	0.77 (0.49–0.91)	0.76 (0.56–0.94)	>0.6
S-zinc (μmol/l)	10.6–18.9	13.3 (10.2–16.8)	17.4 (11.6–22.8)	<0.001	12.5 (8.9–18.3)	12.7 (9.5–15.7)	>0.7
S-vitamin A (μmol/l)	0.90–2.16	1.89 (0.76–3.57)	1.83 (0.76–3.27)	>0.5	1.70 (0.72–2.99)	1.61 (0.66–2.63)	>0.4
S-carotene[a] (μmol/l)	0.76–3.33	1.11 (0.15–3.79)	0.91 (0.16–2.51)	<0.005	1.05 (0.44–3.08)	1.10 (0.32–4.49)	>0.5
Taste score (arb. U)		7.4 (2–11)	10.2 (6–12)	<0.001	7.8 (4–11)	9.0 (3–12)	>0.05

[a] Mean value calculated as the antilog of mean of logarithmic values.
[b] Paired *t*-test. [c] Unpaired *t*-test.

other hospital, and to severe gastric pain after ingestion of zinc tablets, respectively.

Blood tests were performed at two- or six-week intervals (Table I, Fig. 1). Furthermore, at the entry and at the end of the trial, leucocytes, serum (S) protein, plasma (P) sodium, P-potassium, S-creatinine and P-IgM levels were estimated. S-zinc was determined by atomic absorption spectrophotometry, S-vitamin A and S-carotene (α and β forms) by a photometric method (Medicinsk laboratorium A/S, Copenhagen). Blood samples were drawn between 1 and 2 p.m., after at least 4 hours' fasting.

The dark adaptation was measured before and after the trial by means of the Goldmann-Weeker adaptometer. The absolute threshold for light perception was determined after 15 min stay in darkness without any preadaptation. The scores of 200 normal military pilots tested under similar conditions were used as reference values. A performance was classified as being normal, borderline or abnormal.

The colour vision was evaluated by Ishihara's test for colour blindness and further by the pseudoisochromatic plates (AO H-R-R) tritan and tetratan plates in Hard, Rand and Rittler.

At each visit to the clinic the taste function was determined semiquantitatively by a modification of the method described by Krarup (6). The patient was to recognize sweet, salt, sour and bitter by tasting increasing concentrations of sucrose (4, 10 and 40%), sodium chloride (2.5, 7.5 and 15%), citric acid (1, 5 and 10%) and quinine chloride (0.075, 0.5 and 1%). The solutions were presented in a random order, except for the quinine series, which always came last. One drop of the solution was applied to the middle of the tongue, and the patient was allowed to taste with closed mouth. Three points were

Comparison of zinc and placebo group (p)[c]	
Entry	6 weeks
>0.5	>0.4
>0.6	>0.4
>0.8	>0.6
>0.5	>0.9
>0.3	>0.2
>0.3	>0.05
<0.05	<0.02
>0.6	>0.5
>0.6	>0.9
>0.8	>0.5
>0.3	<0.001
>0.5	>0.4
>0.7	>0.4
>0.6	>0.1

scored if the lowest concentration of the test solution led to identification of the tastant, two and one, respectively, if the middle and the highest concentration was recognized. If the tastant was not identified, no point was scored. The sum of the scores was taken as a measure of the patient's overall taste function. Smokers ($n=10$) were asked not to smoke for three hours prior to the visit to the clinic.

The results were analysed statistically by means of the paired and unpaired t-test. Logarithmic transformation of the results was made if required so that calculations could be based on normal distributions.

RESULTS

Thirty patients completed the trial. When the code was broken, it was found that 16 (5 females and 11 males) had received zinc sulfate, and 14 (2 females and 12 males) placebo. Apart from differences in the pretreatment value of S-bilirubin, the two groups were comparable with respect to biochemical findings (Table I) as well as to past history of liver disease. Both groups had subnormal pretreatment mean values of P-albumin and S-magnesium, and high levels of P-IgG and P-IgA.

Only 23% of the patients (2 in the zinc and 5 in the control group) had slightly lowered S-zinc concentrations, which could be explained in all cases by subnormal P-albumin levels. S-vitamin A was decreased in 10% of the patients (3 in the zinc group), whereas S-carotene was subnormal in 33% (4 in the zinc and 6 in the control group).

Except for an unexplained fall in P-IgG in the placebo group, significant changes in the parameters studied occurred in the zinc-treated patients only (Table I). The changes were found in the levels of S-zinc, P-prothrombin, S-bilirubin, S-alkaline phosphatase and S-carotene, and in the taste function, as depicted in Fig. 1. The changes in S-vitamin A were statistically insignificant (Table I), as were the changes in other tests not included in the table.

The dark adaptation studies failed to reveal any beneficial effect of the zinc supplementation. In the zinc group, one abnormal case and 11 borderline cases (75%) were found before the trial and four abnormal and seven borderline cases (69%) after the trial. In the control group, nine (64%) had borderline values before the trial and four abnormal and six borderline values (71%) after the trial. The difference between the number of abnormal and borderline cases in the zinc group and in the control group and the difference between the changes in the groups were statistically insignificant ($p>0.5$).

Red/green colour blindness was present before and after the trial in four out of the 23 males, which is a little more than could be expected, but inconclusive due to the small population examined. No change in the colour vision was observed during the study, especially not in the yellow/blue component.

Three patients in the zinc group experienced a marked improvement of their well-being within the first month of zinc medication. Their taste score values increased from 7 to 11, 9 to 11, and 5 to 11, respectively. They noticed spontaneously the improved taste function. One of them, a male of 68 years, experienced smell sensations for the first time for many years. S-zinc, S-vitamin A and S-carotene of the patients were essentially normal.

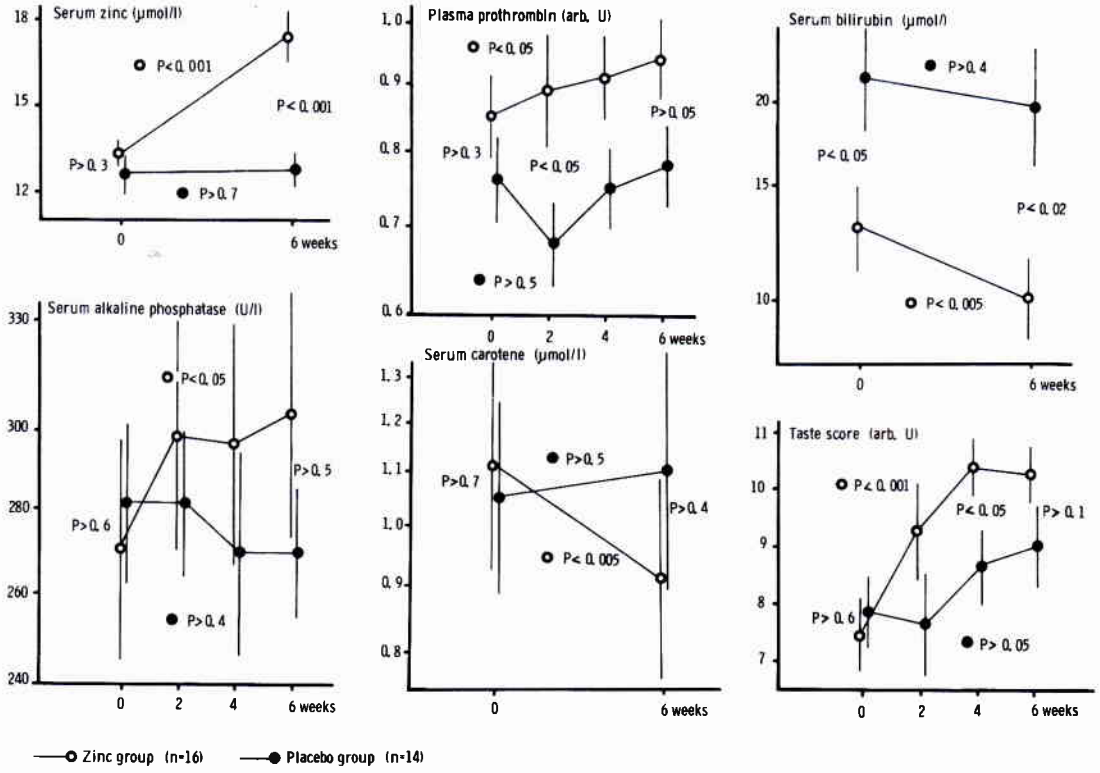

Fig. 1. Comparison of patients receiving zinc supplementation and patients receiving a placebo. Single circles (open and closed) indicate that the p-value is calculated by means of paired t-test of the results of each group before and after six weeks of treatment. Otherwise the p-value indicates comparison between the groups by unpaired t-test. Vertical lines denote S.E.M. Prothrombin, bilirubin, alkaline phosphatase and carotene levels were not normally distributed. In these cases the ordinates are logarithmic and the mean is calculated as the antilog of the mean of logarithmic values. Likewise, the S.E.M. is based on the logarithmic values.

Seven of the 16 patients receiving zinc sulfate complained of transient uneasiness and/or gastric pain shortly after ingestion of the tablets. The discomfort gradually ceased as the medication was continued, except in two patients who suffered from recurrent episodes of diarrhoea throughout the trial. Three patients in the placebo group had slight gastric oppression following tablet ingestion.

DISCUSSION

The present results verify that zinc therapy has some effects in stable alcoholic cirrhosis. As expected, S-zinc of the zinc-treated group rose significantly during the trial and a rise was also seen in the S-alkaline phosphatase activity. The two parameters run a parallel course in the hereditary zinc deficiency disorder acrodermatitis enteropathica (19), in conditional zinc deficiency due to long-term zinc-free parenteral nutrition (20) and in chronic zinc deficiency of beer drinkers with chronic alcoholism and malabsorption (21). Simkin (12), who gave oral zinc sulfate to rheumatoid arthritics, also noted a rise in the S-alkaline phosphatase activity of his patients. Determinations of alkaline phosphatase isoenzymes were not performed systematically in that or in the present investigation. So, it is still not known whether the fluctuations primarily occurred in liver-type, bone-type or intestinal-type alkaline phosphatase. The mechanism of action of this zinc effect is unknown but it is probably relevant that the alkaline phosphatase enzyme, as isolated from Escherichia coli (11), is a zinc metalloenzyme. As the phenomenon has been reported only in disease states connected with zinc deficiency, it can perhaps be taken as evidence of latent zinc deficiency in our patients. In this study it seems unlikely that the rise in S-alkaline phospha-

tase activity was related to cholestasis, as at the same time S-bilirubin decreased significantly in the zinc-treated group. A toxic effect of zinc sulfate on the liver cells seems unlikely, and the mean level of S-alanine aminotransferase also remained unaltered within the reference limits.

Weser et al. (23) have shown that rat liver RNA polymerase and the synthesis of liver RNA and protein are stimulated by supplemental zinc. If this holds true for humans too, it might explain the significant increase in the prothrombin level of the zinc-treated patients, but not the fact that the P-albumin concentration of the patients remained unaltered low during six weeks of zinc supplementation. Six weeks of therapy, however, may be too short to evaluate such an effect of zinc. It was studied because in various mammalian species zinc deficiency produces alterations in albumin and gamma globulin plasma levels (7, 9), not unlike those found in cirrhosis of man.

We were unable to confirm any beneficial effect of zinc on the dark adaptation of cirrhotics, as recently reported by Morrison et al. (8). This might be due to the relatively good vitamin A and zinc nutrition of our patients, as evaluated from the normal pretreatment serum levels of these elements. It might also be related to the examination method used which, particularly with untrained persons, is influenced by a large variability that conceals minor changes in the adaptation function.

The normal S-vitamin A level of the zinc-treated patients remained unchanged during the trial, whereas a marked fall was observed in the S-carotene level, Morrison et al. (8) reported normal S-carotene but highly decreased S-vitamin A levels in cirrhotics with significantly lowered S-zinc values. The low S-vitamin A levels reported, probably reflected a decreased concentration of plasma retinol-binding protein, as often found in cirrhosis, (13), but it might also be related to a disturbed conversion of carotene to vitamin A. Further studies will clearly be needed to clarify the possible role of zinc in the interconversion of carotene to vitamin A. It is well known that zinc is involved in the metabolism of vitamin A. Alcohol dehydrogenase is a zinc metalloenzyme (16), which in combination with NAD (cozymase) also catalyzes the conversion of vitamin A, or retinol, to retinal, which combined with opsin constitutes rhodopsin. Retinal oxidase, which converts vitamin A alcohol to retinoic acid in the tissues, is another zinc-dependent enzyme (16). Furthermore, zinc seems to play an important role in the synthesis by the liver of retinol-binding protein (15). It is not known whether zinc is specifically involved in the synthesis of opsin in the retina.

Cirrhosis is often associated with abnormalities of the smell and taste functions (1). A relation to abnormalities in zinc, copper and vitamin A metabolism has been proposed, but is still unclear. The positive response to zinc supplementation in the present study suggests that zinc is involved, but other factors may play a role, too. Since idiopathic loss of taste is correctable by zinc, copper and nickel supplements (4), the improvement of the patients' taste function by zinc cannot be taken as evidence of pre-existing zinc deficiency.

Kahn et al. (5) reported that the degree of aberrant zinc metabolism in cirrhosis seems to be correlated to the severity of liver dysfunction. All cirrhotics of the present study were in a stable phase, and none showed evidence of a decompensated liver function. This probably explains their overall normal S-zinc values. This, however, does not exclude low zinc levels in the tissues and in diseased organs such as the cirrhotic liver. Beneficial effects of the zinc supplementation on some liver parameters were observed, and it might be speculated that severely affected cirrhotics, especially those with a high alcohol intake, would benefit more from zinc therapy. Clinically overt zinc deficiency has been reported in cirrhotics mainly living on alcohol and beer, which happen to be extremely poor in zinc (21, 22). In such cases zinc has an impressive effect on zinc-related skin symptoms such as widespread eczema craquelé, dermatitis on the acral parts of the extremities (acrodermatitis) and in the anogenital region, as well as on the poor hair growth (21, 22). The present results suggest that zinc also has positive effects in cirrhotics without such evidence of zinc deficiency.

The question of routine administration of zinc in alcoholic cirrhosis must await clarification by further research.

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