Zinc absorption in Crohn's disease

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SUMMARY Zinc deficiency is a potential complication of Crohn's disease and we have searched for evidence of this and assessed the possibility that malabsorption of zinc might be a cause. Serum zinc concentrations in 33 patients suffering from Crohn's disease were significantly lower than in 58 normal control subjects ($9.18 \pm 2.3 \mu\text{mol}$ compared with $13.6 \pm 1.73 \mu\text{mol}$, $P < 0.0005$). Serum zinc correlated well with serum albumin concentrations and the low serum zinc may simply reflect the low serum albumin. Thus its value as an indicator of zinc deficiency is poor. We studied zinc absorption in seven patients with Crohn's disease and compared it with the results obtained previously in five normal subjects using a new technique involving a short-lived isotope of zinc (^{65}mZn). Plasma appearance curves, constructed after an oral dose of isotope, and disappearance curves, after an intravenous dose, were used in a deconvolution computer programme to calculate zinc absorption. Compared with normal subjects, zinc absorption was considerably impaired in patients with Crohn's disease (range 8-45%, compared with 38-75%). This abnormality is a potential cause of zinc deficiency in patients with Crohn's disease.

Zinc is an essential element in plants, animals, and man.^{1,2,3} It has been demonstrated to be a constituent of about 70 metallo enzymes which participate in many metabolic processes.^{4,5} There is growing evidence that deficiency of zinc may be responsible for manifestations of disturbed health including hypogonadism, dwarfism, poor wound healing, and a variety of skin rashes.⁶⁻⁸ Acrodermatitis enteropathica, a rare inborn error of metabolism, is associated with many of the manifestations of zinc deficiency which respond to zinc therapy.⁹⁻¹⁰ Zinc deficiency has been recognised in Crohn's disease and it is possible that it is responsible for some of the manifestations of the disease, such as malaise, poor wound healing and rashes.¹¹ The mechanisms by which zinc deficiency may occur in this disease include anorexia with reduced intake, decreased absorption, or increased loss. The present investigation was performed to search for evidence of

zinc deficiency in a group of patients with Crohn's disease and to assess whether malabsorption of zinc occurred in this condition.

Methods

Sera were obtained from 33 patients (male 16, female 17) suffering from active Crohn's disease, the diagnosis being based on clinical, radiological, and histological criteria. The results of serum zinc measurements in these patients were compared with zinc measurements in a control group of 58 healthy normal volunteers. Both groups had fasted from midnight and samples were taken between 9 am and 10 am. The mean ages were 35.5 years for the patients (range 15-70 years) and 33 years for the normal subjects (range 20-48 years).

Serum zinc was measured by atomic absorption spectrophotometry (Pye Unicam) and, to avoid the possibility of contamination, plastic syringes and plastic tubes were used for blood collection.¹² Haemolysed samples were discarded. One millilitre of serum was diluted with 9 ml distilled and deionised zinc free water. Measurement of zinc believed to be bound to α_2 macroglobulins was performed using PEG 6000.¹³ This material precipitates proteins with molecular weights of more than 100 000 daltons and zinc concentrations were determined in the

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Table Clinical details of patients in whom zinc absorption tests were performed

Patient	Age (yr)	Sex	Disease site	Disease activity	Hb (g/dl)	S. folate (μ g/l)	S. albumen (g/l)	Faecal fat (mmol free fatty acid/day)	S. Zn (μ mol/l)	Zn absorption (%)
1	31	M	Jejunum + ileum	Remission	10.2	18	38	24.6	3.67	27.5
2	18	M	Ile-ectomy + hemicolectomy	Remission	11.4	8	44	—	10.4	16.2
3	32	M	Ileum + colon	Active	9.6	6.4	30	39.8	7.5	22.6
4	36	M	Ileum + colon	Active	12.1	3.1	31	42.3	6.89	33.6
5	54	M	Ileum + hemicolectomy	Remission	12.1	5.0	41	—	10.1	45
6	31	M	Jejunum + ileum	Moderately active	10.8	1.6	32	—	6.58	12.3
7	40	F	Jejunum + ileum	Active	9.1	1.0	30	73.9	5.81	8

supernatant after such precipitation. This figure, subtracted from total serum zinc concentrations, provides an indication of the proportion of zinc bound to α_2 macroglobulin.

Plasma albumin was determined by cellulose acetate protein electrophoresis.

Urine zinc concentrations were measured, without dilution in aliquots of 24 hour collections.

Zinc absorption was measured in seven patients with Crohn's disease of the small bowel using an isotope method previously described.¹⁴ Clinical details are shown in the Table. Briefly this test involves the administration of a tracer dose of the short-lived isotope ^{69m}Zn (half life 13.9 hours)* by mouth with 2 mg cold zinc. Appearance of radioactivity in peripheral blood was measured at frequent intervals over eight hours and a curve of uptake was constructed. One or two weeks later an intravenous injection of isotope was given and the rate of disappearance of radioactivity from the blood was determined over eight hours. With a computer deconvolution programme the 'appearance' and 'disappearance' curves were used to calculate the absorption rate. The dose of isotope used orally was 50 μCi , and intravenously, 25 μCi . Subjects were fasted overnight and the oral dose was given without food. A standard lunch was allowed three hours after the test was started. Radioactivity was measured with an automatic well-type gamma counter (LKB Wallac). The results of these tests were compared with those we have obtained previously in five normal subjects.¹⁴

Results

SERUM ZINC CONCENTRATIONS

In a group of 58 normal subjects the mean serum zinc concentration was $13.6 \pm 1.73 \mu\text{mol/l}$ compared with the group of 33 Crohn's patients in

which the mean concentration was $9.18 \pm 2.3 \mu\text{mol/l}$ ($P < 0.005$). There was no obvious relationship between these values and the sex or age of the patients. Serum zinc concentrations correlated well with serum albumin concentrations (correlation coefficient of 0.6). That the reduced serum zinc concentration was related to serum albumin was further borne out by measurement of the proportion bound to α_2 macroglobulin. There was no significant difference in the macroglobulin bound concentration between Crohn's and control groups (5.43 ± 1.45 and $5.43 \pm 1.45 \mu\text{mol/l}$ respectively), the major part of the difference in total zinc concentrations being attributable to the remaining portion bound to albumin (6.59 ± 2.06 against $9.46 \pm 2.3 \mu\text{mol/l}$ in the Crohn's and control groups respectively).

Fig. 1 Plasma appearance curves after an oral dose of ^{69m}Zn . The range in five normal subjects is shown in the shaded area.

*Radiochemical analysis of this isotope revealed trace amounts only of contaminants: with $^{69m}\text{Zn} \equiv 100\%$, $^{69}\text{Zn} = 0.81\%$, $^{64}\text{Cu} = 0.14\%$, $^{24}\text{Na} = 0.22\%$, $^{42}\text{K} = 1.3\%$, $^{152}\text{Eu} = 3.1\%$ ($T_{1/2} = 9.32\text{h}$). The analysis was performed by Dr J D Hemingway, Universities Research Reactor Risley.

Urine zinc excretion in 23 patients with Crohn's disease ranged from 19.9 to 136.2 $\mu\text{mol}/24\text{h}$ with a mean value of 43.3 $\mu\text{mol}/24\text{h}$. This compares with a reported normal range of 32.1 to 123.2 $\mu\text{mol}/24\text{h}$ (mean 76.5) in 20 subjects.¹⁵ These values are much less than in a group of 12 cirrhotic patients in whom we found a mean excretion of 203.5 $\mu\text{mol}/24\text{h}$.

ZINC ABSORPTION STUDIES

After the oral dose of $^{69\text{m}}\text{Zn}$ all but one of seven Crohn's patients had lower serum appearance rates than any of the five normal control subjects (Fig. 1). There was also a delay in the peak appearance in three Crohn's patients.

After the intravenous dose of $^{69\text{m}}\text{Zn}$ the rate of disappearance of radioactivity from serum in most patients was similar to that previously found in normal subjects, but in three elimination was more rapid and in one slightly delayed (Fig. 2).

Net zinc cumulative absorption, calculated by a deconvolution computer programme from radioactivity appearance and disappearance curves, was significantly lower in the seven Crohn's patients than in the five normal subjects (Fig. 3). The range in the patients was 8–45% and in the normal subjects 38–75%.

Fig. 2 Plasma disappearance curves after the intravenous injection of $^{69\text{m}}\text{Zn}$. The normal range is again shown in the shaded area.

Fig. 3 Cumulative absorption of $^{69\text{m}}\text{Zn}$ calculated by a computer deconvolution programme. The normal range is shown in the shaded area.

Discussion

These studies confirm that serum zinc concentrations are often lower in patients with Crohn's disease than in normal subjects and that this reduction correlates well with the lower serum albumin concentration.¹¹ The likelihood is that the low serum zinc simply reflects serum albumin reduction rather than deficiency. Thus measurement of serum zinc is unlikely to be of much help in detecting deficiencies in these patients. Unfortunately the assessment of zinc stores is difficult. Measurement of zinc content in hair and nails, originally thought to provide an indication of body stores,¹⁶ has also been shown to be unreliable.^{11,17} A simple reliable test is not available and we will have to rely on clinical suspicion in most cases where the possibility of zinc deficiency arises.

It is reasonable, however, to believe that zinc deficiency is a potential complication of intestinal diseases such as Crohn's disease. This could result from inadequate intake, due to anorexia, or from increased elimination or from malabsorption.

It has been reported that increased urinary losses of zinc in cirrhotic patients plays a role in their zinc deficiency.^{15,18} This mechanism was unlikely

to be relevant in our patients with Crohn's disease, however, as urinary losses were not excessive, and were much lower on average than in our cirrhotic patients.

There was some evidence for an increased rate of elimination of zinc from the blood after intravenous injection in some of the patients. This could indicate an increased rate of loss of zinc from the body—into the intestinal lumen, for example—but equally could be due to loss from plasma into zinc-depleted tissues. Thus the case for increased elimination as a cause for deficiency is unproven.

The isotopic test of zinc absorption, however, suggests that absorption was impaired in these patients compared with our previously studied normal subjects.¹⁴ Care has to be taken in the interpretation of tests of absorption which utilise the technique described here, however, as orally administered substances may be handled differently from when they are given intravenously. Plasma curves obtained after oral administration will be modified by prior passage of the substance through the liver. However, significant errors are likely only where there is considerable extraction or metabolism of the substance during the first passage through the liver. In the case of zinc this is unlikely to be a major source of error in normal subjects. It is conceivable, however, that, in the Crohn's patients, a different rate of extraction during first passage would change the calculated 'absorption' and make comparisons with normal subjects suspect. We believe that this is unlikely to be a significant source of error, as the apparent *impaired* absorption will result only from *increased* extraction during first passage through the liver. This might conceivably occur if hepatic stores were depleted but, in this case, clearance after intravenous administration should be more rapid too. Only three of our subjects showed this response, while the others had a normal or delayed clearance. We believe therefore that these results do suggest that zinc is absorbed poorly in Crohn's disease.

The possibility arises that this test with isotopic inorganic zinc does not reflect absorption of zinc in food and this cannot be excluded.

Despite these possible sources of error, however, this test of zinc absorption is an improvement on previously reported methods in that it employs a short half-life isotope technique with which the radiation hazard is much less than with the long half-life ⁶⁵Zn (half-life 265 days).^{19, 20} It is much simpler and quicker than metabolic balance studies²¹ and can be performed on ambulant patients.

The malabsorption demonstrated here could lead to a deficiency of zinc which might play a role in such clinical manifestations as poor wound healing,

skin rashes, and impaired gonadal function. In the absence of a good test of zinc deficiency a clinical suspicion of deficiency in Crohn's patients should be aroused early. It is a simple matter to supplement zinc intake where such a deficiency is suspected.

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