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# Investigation of the Zinc Status of Surgical Patients

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**Abstract**—Zn kinetics were studied in two surgical patients and compared with the findings in three controls. One patient had malabsorption following resection of part of the small intestine, the other was suffering from malabsorption due to radiation enteropathy incurred more than 10 years earlier. Whole-body retention of i.v. administered $^{65}Zn$, measured with a simple linear scanner, showed a sharp initial drop in the first patient, followed by an increased retention. This was explained by large initial intestinal losses of Zn leading to a state of Zn deficiency. In the second patient, who had developed Zn deficiency over a period of years, the whole-body retention was increased from the beginning. Compared with other parameters, whole-body retention seems to be a good indicator for the Zn status of patients, although of limited clinical use because the measurements take too much time.

## Introduction

The importance of zinc for plants and animals has been known for several decades. In 1934, Hart and collaborators showed this for animals.[1] From the work of Prasad and others it is now known that zinc is also essential for man (for review, see Refs 2 and 3). Zinc deficiency has a negative influence on various aspects of human health. It can be caused by: (a) an insufficient dietary supply, i.e. a daily dietary intake considerably lower than the recommended dietary allowance (RDA) (15 mg per day for non-pregnant, non-lactating adults); (b) decreased absorption from the gastrointestinal (GI) tract as in the short-bowel syndrome; and (c) excessive losses, either in the stool as in protein losing enteropathy or in the urine due to the administration of complexing agents such as amino acids (during total parenteral nutrition) or medication, e.g. penicillamine.

Clinically, two main types of zinc deficiency can be distinguished, a chronic and an acute form. The former is characterized by growth retardation and hypogonadism and is usually of dietary origin. The first cases of zinc deficiency described in man were of this type.[4] In the latter form the symptoms include skin lesions, diminished taste and smell perception, alopecia, retarded wound-healing, and diminished cellular immune defense. Causes include omission of zinc from total parenteral nutrition and severe losses as in Crohn's disease.

A special form of Zn deficiency is acrodermatitis enteropathica, a hereditary disorder affecting Zn absorption from the GI tract, in which the most pronounced symptoms are chronic diarrhea, skin lesions and alopecia.[5]

From the literature no single parameter can be considered to indicate satisfactorily the Zn status of patients under various conditions.[3] In particular the plasma Zn concentration is influenced by various conditions unrelated to the Zn status, such as the time since last food intake, infection, and abnormal plasma protein values (for which corrections sometimes can be made). One of the most conclusive tests appears to be the whole-body retention of $^{65}Zn$ and the biological half-life of this nuclide, calculated from these data.[6,7] However, it takes rather long, weeks or even months, to measure this half-life reliably in man. Therefore, in our study the parameters of the whole-body retention of $^{65}Zn$ in two patients were compared with other data such as the plasma and urine levels of Zn, $^{65}Zn$ plasma clearance and the results of the oral $^{69m}Zn$ loading test, to see whether, retrospectively, the whole body-retention data collected during the first weeks after administration of $^{65}Zn$, could be useful and yield information about the Zn status of the patient.

In this paper the results of the investigation of two patients in whom Zn deficiency was suspected are reported and compared with similar data of three apparently healthy volunteers. Clinical data of these patients are presented in their case histories below.

## Materials and Methods

$^{65}Zn$ was commercially obtained from The Radiochemical Centre (Amersham, U.K.). $^{69m}Zn$ was produced in the reactor of the Interuniversity Reactor Institute (Delft, The Netherlands) by irradiating enriched $^{68}Zn$ with thermal neutrons. This was followed by purification steps consisting of absorption on and elution from Dowex-2.

The $^{65}Zn$ was injected intravenously as the acetate in a volume of 3 mL containing 0.33 mg total Zn and 5 $\mu$Ci $^{65}Zn$.

Whole-body retention was determined by slowly moving the patient on a bed between two NaI-detectors (3 × 2 in.) fitted with wide-angle collimators. Counts of both detectors were registered and, after correction for background counts, compared with those of a phantom containing a known fraction of the dose. Retention was expressed as percentage of the dose.

The Zn in the body can be described as an open two-compartment system (Fig. 1, bottom). When $^{65}Zn$ enters the body by either the oral or the i.v. route, it first mixes rapidly with the Zn in pool 1, from where it will slowly equilibrate with the Zn in pool 2. Pool 1 comprises, among other things, the albumin-bound Zn of the blood circulation, pool 2 the Zn in muscle and bone tissue. Excretion of Zn (and $^{65}Zn$) in urine and feces originates from pool 1. On the basis of this model, the whole-body retention of i.v. injected $^{65}Zn$ ($R$) can be described as the sum of two exponential expressions[6] (Fig. 1, top):

$$R = a_1 * \exp(-b_1 * t) + a_2 * \exp(-b_2 * t)$$

in which:
$R$ = percentage of $^{65}Zn$ still present in the body at time $t$; $a_1, a_2$ = percentages of the total body content at $t = 0$, retained via the fast and the slow phases, respectively; $t$ = time (in days); $b_1, b_2 = \ln 2/t_{1/2}(1)$ and $\ln 2/t_{1/2}(2)$, respectively; $t_{1/2}(1), t_{1/2}(2)$ = half-life of the fast and slow phases, respectively (in days). The constants of these expressions ($a$'s and $b$'s) were computed for each patient with an iterative technique for least-squares estimation of non-linear parameters.[8]

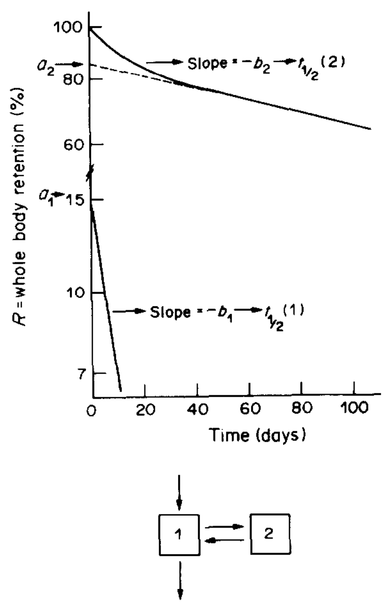


Fig. 1. Top: Example of a whole-body retention curve obtained after i.v. injection of $^{65}Zn$. Also shown are the computed curve of the slow (slope: $-b_2$) and of the fast (slope: $-b_1$) phase. The latter was arrived at by deducting the curve of the slow phase, extrapolated to time $t = 0$ (dashed line), from the actual retention curve. Bottom: Schematic representation of an open two-compartment system.

Plasma $^{65}Zn$ disappearance curves were constructed from data obtained by measuring the plasma $^{65}Zn$ activity, using a well-type NaI crystal, for a period of 6 h after the i.v. injection of the nuclide. Values are expressed as percentage of the dose in the total plasma volume, assuming that this amounts to 4.4% of the body weight.

For the $^{69m}Zn$ loading test, 60 $\mu$Ci $^{69m}Zn$ was orally administered as the acetate in 50 mL 50 mM acetate buffer (pH 5.6) containing 50 mg Zn. The plasma curve was obtained in the same way as for to the $^{65}Zn$ disappearance curves.

Urinary $^{65}Zn$ was measured with a large volume-counter equipped with two NaI-detectors (3 × 2 in.). Values are also presented as percentage of the dose.

The total Zn content of plasma and urine was measured by flame atomic absorption spectrometry. For all other determinations standard clinical chemistry methods were used.

The study comprised of two female patients with malabsorption and three healthy male controls, aged 28, 50 and 54 yr. Informed consent was obtained from all subjects.

## Case Histories

Patient 1, a woman born in 1955, was operated on for acute abdominal symptoms (March 1981). Necrosis of a large part of the small intestine, due to mesenteric thrombosis, was found. Resection of the necrotic part of the small intestine, which extended from 90 cm past the ligament of Treitz to 10 cm before Bauhin's valve, was necessary. Postoperatively she developed severe diarrhea which could be controlled after 6 weeks with dietetic measures. During this episode, she lost 14 kg body weight. Four months later she had developed erythematous skin lesions on both legs and was losing hair. Her body weight was 50 kg, and laboratory investigation revealed malabsorption (fat excretion was 11 g or more per day; the Schilling test showed disturbed vitamin $B_{12}$ absorption). Plasma Zn was 0.4 $\mu$g/mL, urine Zn about 100 $\mu$g/24 h (Fig. 2). Oral supplementation with zinc sulfate was prescribed but, as later turned out, she discontinued this therapy after a few days, because of gastro-intestinal distress.

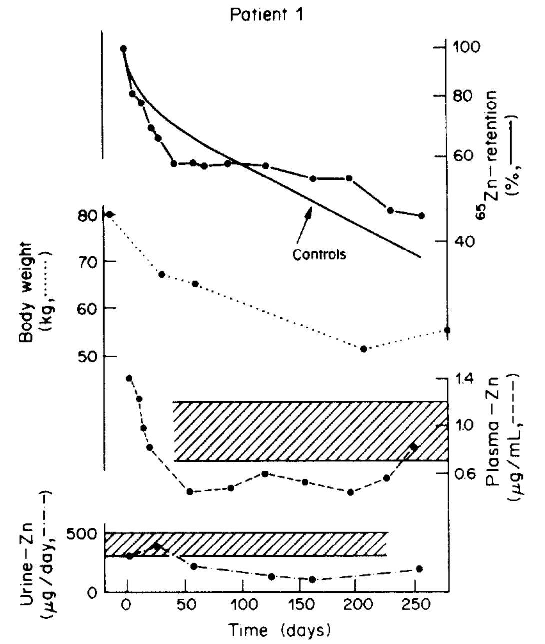


Fig. 2. Whole-body retention curve and body-weight, plasma-zinc and urine-zinc of patient 1 as function of time after an i.v. dose of $^{65}Zn$. The best fitting curve for the average results of whole-body retention of three controls is shown as a smooth line. Normal values of plasma-zinc and 24-hr urine-zinc are shown as shaded areas. Note: The vertical axis does not coincide with time $t = 0$ on the horizontal axis.

Additional dietetic measures and vitamin supplemention resulted in stabilization of her condition. February 1982 her body weight was 52.4 kg and her plasma-Zn had risen to 0.80 $\mu$g/mL. Skin lesions and hair loss had subsided, and her general condition had improved. The investigation of her Zn status was started 3 weeks after the operation by administration of an i.v. dose of $^{65}Zn$.

Patient 2 was a women born in 1914. In 1970, a malignant ovarian tumor was removed, followed by radiotherapy. In July 1971, a laparotomy was performed because of internal obstruction. No obstructing adhesions were seen, but severely edematous and fibrotic sections of both the small intestine and the colon were found. The condition was diagnosed as radiation enteropathy and resection was not judged advantageous. She had severe steatorrhea, with a loss of 15–45 g fat per day, and malabsorption was apparent. In 1981 (viz. 10 y after the surgery and radiotherapy), she was readmitted for a short time because of progession of the malabsorption, possibly the first sign of a non-Hodgkin lymphoma diagnosed later. Total plasma protein and albumin were low (24 and 14 g/L, respectively) and her body weight and plasma Zn level had dropped (Fig. 3). An investigation of the Zn status using $^{65}Zn$ was started in July of 1981. The absorption of an oral dose of $^{69m}Zn$ was measured in October of 1982 (Fig. 3), shortly before a non-Hodgkin lymphoma was diagnosed. After further deterioration of the general condition she died in November 1982.

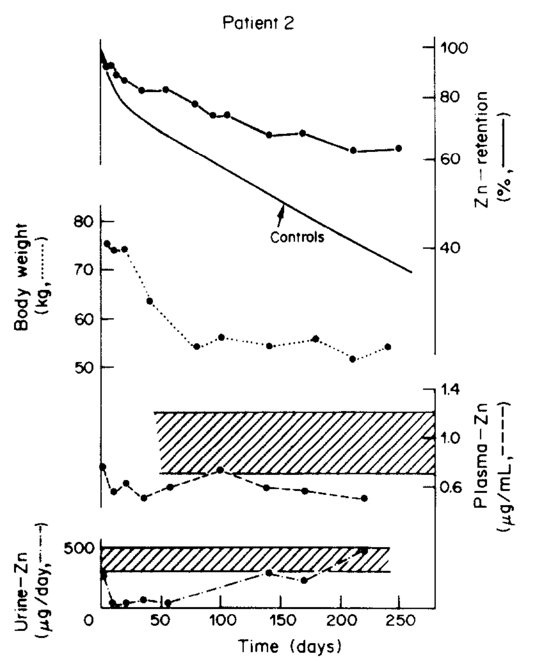


Fig. 3. Whole-body retention curve and body-weight, plasma-zinc and urine-zinc of patient 2 as function of time after an i.v. dose of $^{65}Zn$. Other details as in Fig. 2.

## Results

The whole body $^{65}Zn$ retention curves of both patients (Figs 2 and 3) are compared with the best fitting curve for the average results of three controls. The constants calculated for the exponential expressions are shown in Table 1. The values for the controls agree with those of Arvidsson *et al.*[7] who, after i.v. administration of $^{65}Zn$ to 8 controls, found a mean value of 85% for $a_2$ and 9 and 248 days for $t_{1/2}(1)$ and $t_{1/2}(2)$, respectively.

Plasma-disappearance curves of the $^{65}Zn$ of the two patients are shown in Fig. 4 together with those of 3 controls given for comparison.

The oral plasma $^{69m}Zn$ loading test was only performed in patient 2 and the result is also shown together with those of the 3 controls (Fig. 5).

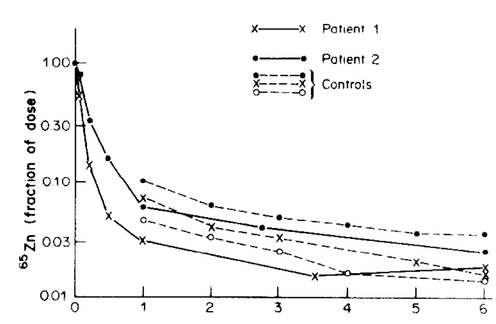


Fig. 4. The $^{65}Zn$ plasma-disappearance curves of patients 1 and 2 and of three controls.

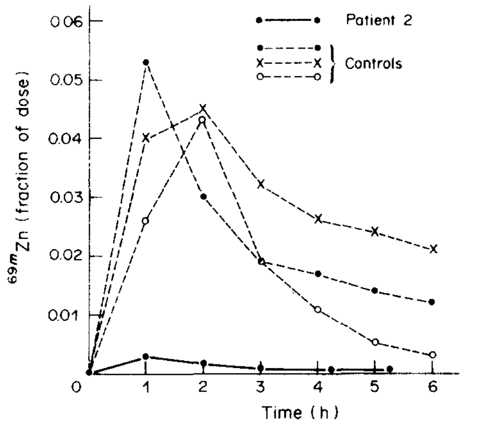


Fig. 5. The oral $^{69m}$Zn loading test of patient 2 and of three controls.

Data on the $^{65}$Zn and total Zn concentrations in plasma and urine and some chemical laboratory data for both patients are given in Table 2.

## Discussion

Patient 1 showed a rapid initial decrease of whole body $^{65}$Zn after an i.v. dose of $^{65}$Zn (Fig. 2; Table 1). Since the cumulative urinary excretion of $^{65}$Zn during the first 10 days after i.v. injection was only 2.4% of the dose and no evidence was obtained that the pools involved had changed in volume, much of the parenterally administered $^{65}$Zn must have been lost in the feces. In all probability this loss was due to excretion of Zn in the pancreatic juice.

Because there is no reason to assume that the intestinal excretion had increased, the net loss of Zn must have been caused by a diminished reabsorption capacity of the remaining (short) intestinal tract.

When muscle tissue is wasted, Zn is set free. According to Fell,[9] in such cases the Zn is superfluous and is excreted by the kidneys. This was not the case in patient 1, who lost 14 kg of her body weight during the first 6 weeks after operation. Assuming that one-third of the lost body weight was lean body mass and that muscle tissue contains 60 $\mu$g Zn/g wet weight,[10] the amount of Zn mobilized per day would have been 8 mg. Apparently in her case the Zn was not superfluous but needed to compensate for the pancreatic loss, which under normal conditions is about 8 mg per day.[11]

From the $^{65}$Zn whole body retention curve it is clear, however, that the sum of Zn, stemming from catabolism and of reabsorbed Zn, was not sufficient to compensate for the total loss of Zn. After the initial rapid disappearance of $^{65}$Zn, a new steady state was reached with low values for the plasma and urine Zn content. The remaining $^{65}$Zn was then retained with a biological half-life ($t_{1/2}$) of 1140 days, which is indicative for Zn deficiency.

After about 180 days the whole body retention curve of patient 1 showed a steeper slope (Fig. 2). This coincided with an improvement of her clinical condition (see under "Case Histories") and an increase of body weight and the plasma Zn concentration (Fig. 2). This improvement was obviously spontaneous, since the intended Zn suppletion turned out to have been omitted by the patient because of GI complaints. The improvement should therefore be attributed to hyperplasia of the villi of the small intestine. This hyperplasia probably improved the absorption of dietary Zn and caused, by gradually improving the Zn status, a change in the whole body retention of $^{65}$Zn similar to that described by Aamodt *et al.*,[12] who also produced an increase in slope by treating patients with oral Zn sulfate.

The plasma $^{65}$Zn disappearance curve of patient 1 shows a sharper initial drop than those of the controls (Fig. 4). Since it seems improbable that this patient had already had a Zn deficiency at the start of the investigation, other factors must have been responsible. A likely explanation is the entry of Zn,

Table 1. Constants of the exponential expressions for the whole-body retention curves and the values of $t_{1/2}$, calculated from the exponents after i.v. injection of $^{65}$Zn*

| | $a_1$ (%) | $b_1$ ($d^{-1}$) → | $t_{1/2}$ (d) | $a_2$ (%) | $b_2$ ($d^{-1}$) → | $t_{1/2}$ (d) |
|---|---|---|---|---|---|---|
| Patient 1 | 41 ± 1 | 0.067 ± 0.005 | 10 ± 1 | 59 ± 1 | 0.00060 ± 0.00016 | 1146 ± 238 |
| Patient 2 | 13 ± 1.1 | 0.065 ± 0.012 | 11 ± 2 | 87 ± 0.9 | 0.00155 ± 0.00006 | 448 ± 18 |
| Controls† | 20 ± 1 | 0.10 ± 0.01 | 7 ± 0.7 | 80 ± 1 | 0.0032 ± 0.0002 | 217 ± 14 |

* $a_1$ and $a_2$: fractional contributions of the two exponential expressions; $b_1$ and $b_2$: slopes of the two exponential curves.

† Mean values of three subjects.

Table 2. Results of urine and plasma analyses after i.v. injection of $^{65}$Zn

| | Plasma zinc ($\mu$g/mL)* | Plasma $^{65}$Zn (% dose)† 1 h | Plasma $^{65}$Zn (% dose)† 5 h | Urine zinc§ ($\mu$g/d)‡ | Urine $^{65}$Zn (% dose/d) | Total protein (g/L)* | Albumin (g/L)* | A.P.¶ (U/L)* |
|---|---|---|---|---|---|---|---|---|
| Patient 1 | 1.43 | 3.4 | 2.4 | 300 | 0.78 | 74 | 33 | 257 |
| Patient 2 | 0.71 | 5.7 | 3.0 | 110 | 0.08 | 57 | 33 | 169 |
| Normal values | 0.7–1.2 | 5–10 | 2–4 | 300–500 | 0.2–1.1 | 62–78 | 35–40 | 60–170 |

* Fasting on first day of investigation. † In total plasma 1 and 5 h after injection. ‡ Averaged over first 10 days of investigation. § Cumulative excretion during first 10 days of investigation. ¶ Alkaline phosphatase.

originating from tissue wasting, into the rapidly exchanging pool 1 (Fig. 1), combined with a loss of Zn, thus causing an increased turnover of plasma-Zn. If this were so, the shape of the plasma-$^{65}$Zn disappearance curve would be indicative of a non-steady situation rather than of a change in Zn status.[13]

The $^{65}$Zn whole-body retention of patient 2 was high from the beginning, in contrast to that of patient 1 (Fig. 3; Table 1). This is in agreement with a state of Zn deficiency after many years of malabsorption and in accordance with the flat oral $^{69m}$Zn absorption curve (Fig. 5). The reduced net loss of $^{65}$Zn must be due to a decreased excretion of $^{65}$Zn by the kidneys and in the gastrointestinal tract. The latter could be partially due to an adaptation to the prolonged state of malabsorption. This is in fact the same phenomenon as seen in patient 1 after the initial rapid loss of $^{65}$Zn.

Despite the already existing abnormal Zn status, the plasma-$^{65}$Zn disappearance curve is in the normal range. This confirms the supposition made above that the shape of these curves does not reflect the Zn status but rather indicates a possible situation of non-steady state.

The present studies shows that whole body measurements of $^{65}$Zn can yield useful information about the Zn status of patients. However, the very long duration of this kind of investigation makes it useless for routine diagnostic purposes. On the other hand, the total plasma-Zn value is not informative, even after correction for low plasma protein, unless this parameter is measured repeatedly and evaluated in combination with the urine-Zn level, over a long period and under steady-state conditions. The $^{65}$Zn plasma disappearance curve is not indicative for the Zn status either as argued above.

It might therefore be of interest to determine retrospectively whether data reflecting the Zn status are available shortly after administration of the $^{65}$Zn. For Example, after 20 days the $^{65}$Zn retention in patient 1 was 68% of the administered dose. Compared to the controls this value is low and can be considered as an indication of Zn loss, although not in the urine, since the cumulative excretion of $^{65}$Zn in the urine was low. In patient 2, low plasma and urine Zn concentrations in combination with a 86% retention of $^{65}$Zn after 20 days, is probably indicative of a prolonged Zn deficiency.

The present data on the Zn kinetics of both patients underscore the importance of the entero-systemic circulation of Zn. In cases with intestinal surgery, particularly involving the resection of large parts of the small bowel, interruption of the entero-systemic circulation causes loss of Zn in the pancreatic juice under the acute conditions, although adaptation to this situation can occur in a basically healthy patient.

Because this study on Zn kinetics was restricted to two surgical patients and three controls, it will be necessary to investigate a large number of patients before extrapolation from early $^{65}$Zn retention data is permissible. On the other hand, the study was performed with a rather simply linear scanner, which means that the availability of a whole body counter is not a necessary pre-requisite for this type of investigation.

## Conclusions

(1) Whole-body measurements of $^{65}$Zn with a rather simple scanner can yield useful information about the Zn status of patients, but because the time required for these measurements is very long, it is not useful in clinical practice.

(2) Disappearance curves of radioactive Zn are not indicative for the Zn status, viz. Zn deficiency.

(3) The oral $^{69m}$Zn loading test is a reliable test for assessment of Zn absorption.

(4) In a state of malabsorption, as part of the short bowel syndrome in the acute situation, one should reckon with a marked loss of Zn in the feces, caused by a disturbed entero-systemic recirculation. This loss may lead to a clinically manifest Zn deficiency, but adaptation appears possible.

(5) Only a combination of parameters such as total plasma and urine Zn, $^{65}$Zn in urine, the results of the $^{69m}$Zn loading test, and the early data obtained by whole-body $^{65}$Zn retention measurements, may yield information about the Zn kinetics. Studies in a larger number of patients could show whether the results of this investigation are indeed useful for clinical purposes.

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