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Serum Zinc and Urinary Zinc Excretion after Renal Allotransplantation

E. CHRISTENSEN & N. MILMAN
Medical Dept. P, Division of Nephrology, Rigshospitalet, Copenhagen, Denmark

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In nine kidney-transplanted patients, receiving prednisone as part of the immunosuppression, serum zinc and urinary zinc excretion were measured for a period of 5–7 weeks after the transplantation. Serum zinc decreased significantly from normal pretransplant values to subnormal values 1–5 days after the transplantation. Thereafter, the serum zinc rose again, and after 2–3 weeks, before start of reduction of prednisone, the serum zinc had risen to a level that was not significantly lower than the pretransplant level. Urinary zinc excretion was generally elevated, especially just after the transplantation. In patients with initially good kidney function the zinc clearance to creatinine clearance ratio was significantly higher during the first week after the transplantation than in the rest of the observation period. Similar findings have been reported after major surgery, and no correlation between serum zinc and the corticosteroid dose was demonstrable. Therefore, in renal allotransplantation, no special supplementation of zinc seems necessary beyond what may be justified by the effect of the surgical trauma.

Key-words: Kidney; serum albumin; transplantation; zinc

E. Christensen, Medical Dept. A, Rigshospitalet, 9 Blegdamsvej, DK-2100 Copenhagen Ö, Denmark

Zinc, a micronutrient essential to man, is considered important to normal wound healing. Zinc deficiency is often associated with delayed wound healing, and zinc supplementation has been followed by acceleration of the healing process (6, 8, 12).

Administration of corticosteroid hormones has long been known to involve delayed wound healing (14, 16). Recently it has been reported that administration of corticosteroids induces a rapid and significant decrease in serum zinc (4).

The possibility might, therefore, exist that the delayed wound healing following corticosteroid administration could be related to zinc depletion.

Since, after renal allotransplantation (RAT), delayed wound healing is a problem of clinical importance, this investigation was undertaken to assess whether the administration of very high doses of corticosteroids, as a part of the immunosuppressive treatment after RAT, induces aberrations in the zinc metabolism, which suggest the necessity of zinc supplementation.

MATERIAL AND METHODS

Nine consecutive necro-kidney-transplanted patients were examined. The immunosuppressive treatment consisted of prednisone and azathioprine. Prednisone was administered just after RAT in a dosage of 120–150 mg/day for 2–3 weeks, whereupon the dosage was gradually reduced during the next 2–3 weeks to a maintenance level of 35–30 mg/day. Threatening

Table I. Clinical data in all patients

Case no.	Sex	Age (years)	Weight (kg)	Kidney disease*	Dialysis before transplantation (months)	Dialysis after transplantation	Graft rejection episodes	Methylprednisolone treatment
Group I								
1	♀	50	43	CP	10	–	–	–
2	♀	49	47	CIN	36	–	–	–
3	♀	30	53	CP	8	–	–	–
Group II								
4	♂	44	50	CG	11	–	–	+
5	♂	30	65	CG	30	–	–	+
Group III								
6	♀	52	45	MN	3	–	+	+
7	♂	37	62	CG	0	–	+	+
Group IV								
8	♀	56	50	CP	22	+	–	+
9	♂	48	55	CIN	5	+	–	–

* CP=chronic pyelonephritis; CIN=chronic interstitial nephropathy; CG=chronic glomerulonephritis; MN=malignant nephrosclerosis.

or manifest graft rejection was treated with intravenous methylprednisolone (Solumedrole®) for 1–4 days in a dosage of 500–1000 mg/day, sometimes followed by a temporary increase of the prednisone dose.

Azathioprine (Imurel®) was administered in a dosage of 5 mg/kg body weight just before the transplantation, followed by a maintenance dosage of approximately 100 mg/day. None of the patients received diuretics.

The patients consumed a standard hospital diet without supplements of zinc. However, the patients with an initially insufficient graft function received a protein-restricted diet containing 40 g of protein per day.

Serum zinc, serum creatinine, and plasma albumin concentrations were determined immediately before RAT (day 0), 4–5 times during the first week and thereafter twice weekly until the prednisone dosage had been reduced to the maintenance level. The 24-hr urine was examined for creatinine, protein, and zinc, when free from blood, with similar intervals after RAT.

Blood samples were drawn in the morning before breakfast, using needles of stainless steel and zinc-free glass. Urine specimens were collected in polyethylene containers.

Zinc was measured on an atomic absorption spectrophotometer (Perkin Elmer, 403) as described by Parker et al. (11). The reproducibility was ± 0.4 μmol/l.

The Wilcoxon and Mann-Whitney rank sum tests and linear regression analysis were used for statistical evaluation of the results.

The nine patients were divided in four groups according to their clinical course.

Group I. Three patients (Cases 1, 2, and 3) with initially good graft function and uncomplicated clinical course.

Group II. Two patients (Cases 4 and 5) with initially good graft function, who, because graft rejection was suspected, received high doses of methylprednisolone.

Group III. Two patients (Cases 6 and 7) with initially good graft function and subsequent rejection episodes treated with methylprednisolone.

Group IV. Two patients (Cases 8 and 9) with initially insufficient graft function due to a long period of ischemia necessitating regular hemodialysis in a period after RAT. One pa-

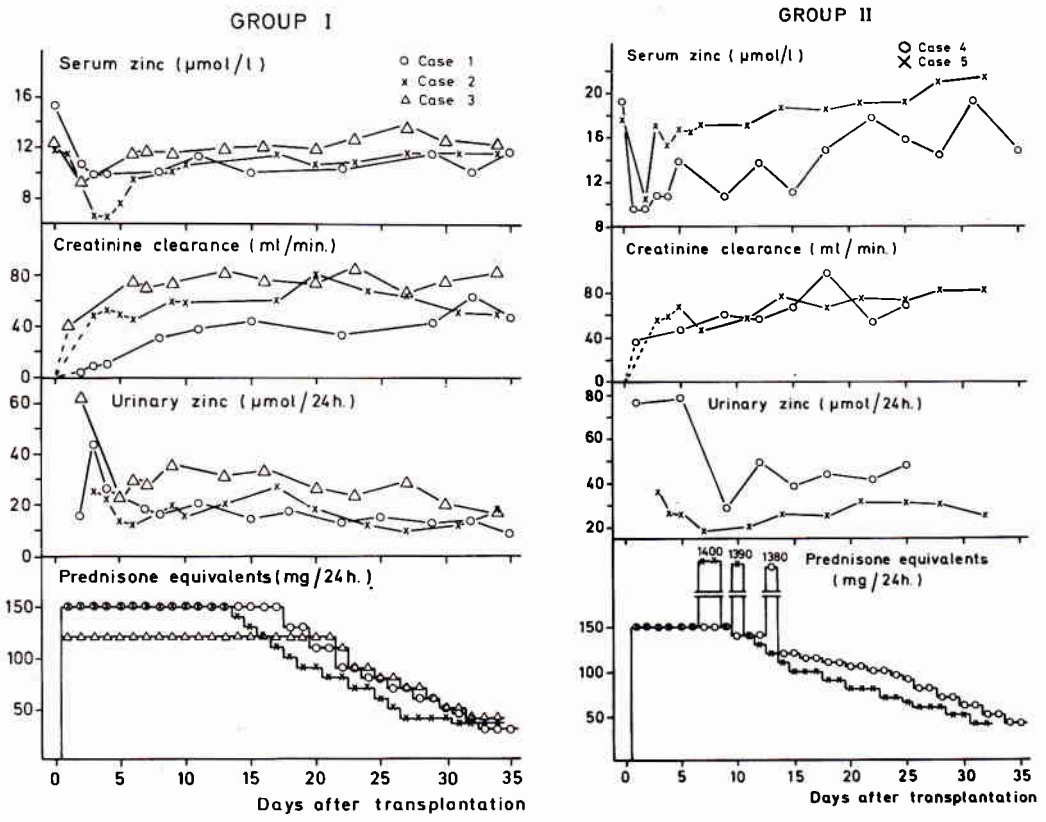

Fig. 1. Serum zinc, creatinine clearance, urinary zinc excretion, and corticosteroid dosage in patients in groups I and II. The corticosteroid dosage is expressed as prednisone equivalents, the effect of 4/5 mg of methylprednisolone being equal to that of 1 mg of prednisone.

tient (Case 8) received methylprednisolone because of suspicion of graft rejection. The other (Case 9) had the graft removed after 13 days because of thrombosis of the graft artery.

Clinical data concerning each patient are shown in Table I.

RESULTS

The results are shown in Figs. 1 and 2 and Table II.

Serum zinc

The median pretransplant serum zinc value was 14.9 µmol/l (range, 11.8–19.3 µmol/l).

In all groups of patients the serum zinc value decreased after RAT, reaching a minimal value within 1–5 days. The median minimal value was 9.3 µmol/l (range, 6.6–10.6 µmol/l). Thereafter the serum zinc increased to a median value of 10.7 µmol/l (range, 9.5–16.4 µmol/l) just before reduction of the steroid dose.

The reduction of the prednisone dosage was not followed by a uniform change in serum zinc. After reduction of prednisone to the maintenance level, the median serum zinc value was 12.6 µmol/l (range, 11.6–21.4 µmol/l).

No significant differences were found between the pretransplant values, the values just before reduction of prednisone, and the values after reduction of prednisone to the maintenance level ($P > 0.05$), whereas all these three sets of values were significantly higher than the minimal values observed on days 1–5 ($P < 0.01$).

The addition of methylprednisolone (Cases 4–8) and the rejection episodes (Cases 6 and 7) did not result in any significant changes of serum zinc.

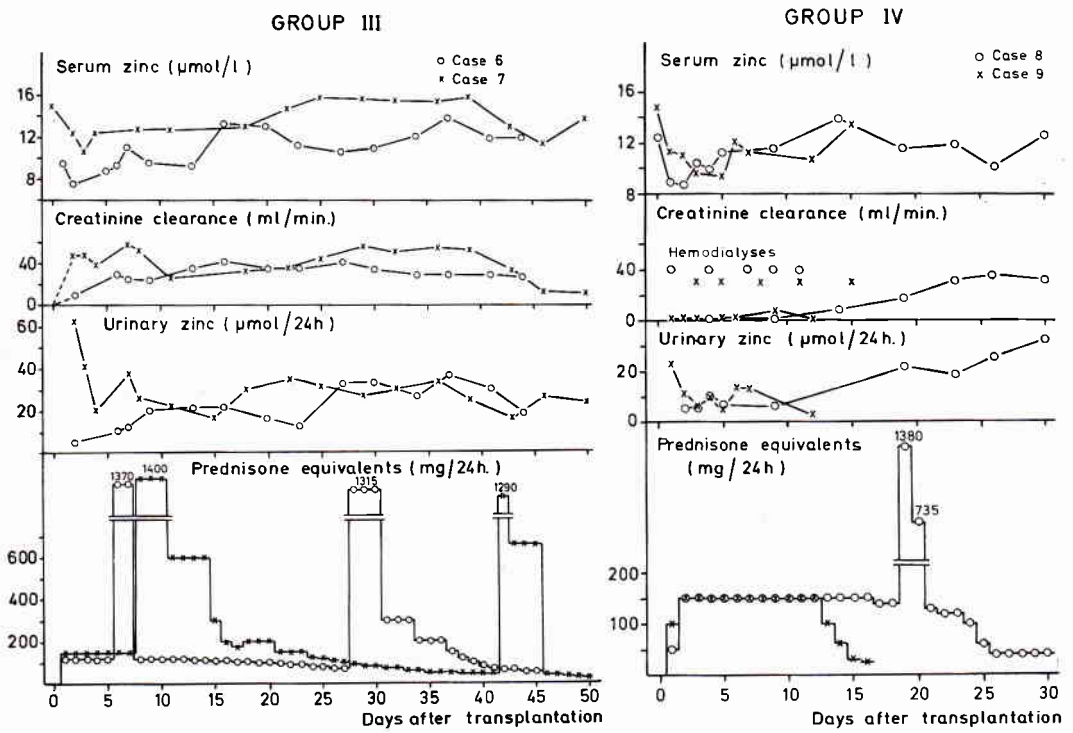

Fig. 2. Serum zinc, creatinine clearance, urinary zinc excretion, and corticosteroid dosage in patients in groups III and IV. See text to Fig. 1.

Accordingly, no correlation between serum zinc and the corticosteroid dosage could be found ($r = 0.009$, $P > 0.05$).

Urinary zinc excretion

In the patients with initially good graft function (Cases 2–5 and 7) urinary zinc excretion was high the first few days after RAT, with values of 25–78 μmol/24 hr. Thereafter, in these patients and in those who later achieved an acceptable graft function (Cases 1 and 6) zinc excretion remained at a rather constant level of about 10–50 μmol, unaffected by the reduction of prednisone dosage. Neither the high doses of methylprednisolone (Cases 4–8) nor the rejection episodes (Cases 6 and 7) involved any consistent change in the urinary zinc excretion.

Urinary zinc concentration was negatively correlated with urine volume ($r = -0.54$, $P < 0.001$).

No correlation between the 24-hr urinary excretion of zinc and of protein (Table II) was demonstrable ($r = 0.10$, $P > 0.05$).

Among the patients who quickly achieved and maintained a creatinine clearance of 35 ml/min or more (Cases 2–5) the zinc clearance to creatinine clearance ratio was significantly higher during the first week after RAT (median, 0.024; range, 0.015–0.11) than during the rest of the observation period (median, 0.017; range, 0.009–0.045) ($P < 0.01$). Daily urine volume was not significantly different in these two periods ($P > 0.10$).

No correlation between the zinc clearance to creatinine clearance ratio and the urine volume was found ($r = 0.11$, $P > 0.10$).

There was no convincing correlation between renal zinc clearance and creatinine clearance ($r = 0.23$, $0.01 < P < 0.05$).

The median plasma albumin levels were subnormal (Table II), and a weakly positive correlation was found between serum zinc and plasma albumin ($r = 0.38$, $P < 0.001$). The mo-

Table II. Urine volume, plasma albumin, urinary protein excretion, and median plasma albumin to median serum zinc ratio in each patient

Case no.	Urine volume (l/24 hr)		Plasma albumin (μmol/l)		Urinary protein excretion (g/24 hr)		Median plasma albumin to median serum zinc ratio (μmol/l/μmol/l)
	Median	Range	Median	Range	Median	Range	
Group I							
1	1.80	0.51–2.58	445	378–575	0.3	0.1–1.5	43
2	3.22	1.75–4.25	435	377–469	0.3	0–2.4	40
3	2.35	1.40–5.00	409	347–469	0.4	0–1.4	34
Group II							
4	2.74	1.90–8.46	417	365–542	0.2	0–3.2	30
5	2.35	1.58–6.78	520	314–639	0.3	0.1–1.6	30
Group III							
6	1.29	0.60–1.93	384	304–414	0.7	0.3–2.9	35
7	3.18	2.50–7.04	410	298–504	2.2	1.2–5.7	31
Group IV							
8	1.64	0.25–4.15	399	291–463	2.2	0.1–4.2	35
9	0.39	0.24–1.30	420	251–518	0.6	0.3–3.8	38
Normal values (95% interval)			532–813		0.0–0.1		

lar proportion between the median plasma albumin and serum zinc values was 30–43.

DISCUSSION

Zinc is established as an essential component of certain metalloenzymes and as cofactor for other enzymes (17). The total body store of zinc is about 30 mmol in the adult (15). The average diet provides 150–240 μmol/day, and about half of this is absorbed (15).

Patients with chronic renal failure usually have slightly lower serum zinc values than normal subjects, the decrease being less pronounced in hemodialyzed than in nondialyzed patients (2, 9).

In all our patients the pretransplant serum zinc values were within normal limits, and serum zinc declined significantly to a minimal subnormal value within 1–5 days after RAT.

Thereafter, the serum zinc began to increase, and just before reduction of the prednisone dosage serum zinc had increased to a level that was neither significantly lower than the level after reduction of the prednisone dosage nor significantly lower than the pretransplant serum zinc level.

In plasma nearly all zinc is bound to protein, only 2–3% being ultrafiltrable (13). A correlation between serum zinc and plasma albumin has been reported by some authors (18), whereas others have failed to find this correlation (2).

We found a weakly positive correlation between serum zinc and plasma albumin. In this context it should be noted that the molar proportion between plasma albumin and serum zinc was about 35, i.e. only about 1/35th of the minimal binding capacity of zinc to albumin was used, provided that other substances did not compete with zinc for the binding site(s). Therefore, a simple correlation between serum zinc and plasma albumin appears unlikely.

The low plasma albumin levels found after RAT were probably caused by increased albumin catabolism due to the combined effects of the surgical trauma (1) and the cortico-

steroid administration (7), whereas proteinuria was not an important factor.

The principal route of excretion of zinc is the feces, chiefly through the pancreatic juice and the bile, whereas urinary excretion is normally of minor importance (15).

In the posttransplantation course the urinary zinc excretion was high, although not of a magnitude that could fully explain the initial decrease in serum zinc. Therefore, an increased zinc excretion by other routes or a shift from the plasma to other body compartments or both of these, must have taken place.

The negative correlation between urinary zinc concentration and urinary volume and the absence of a correlation between the zinc clearance to creatinine clearance ratio and the urine volume indicate that urine volume is not a decisive factor for the urinary zinc excretion.

Gross proteinuria like in the nephrotic syndrome is associated with increased urinary zinc excretion (10). The proteinuria seen in our patients was moderate and not correlated with the urinary excretion of zinc.

In patients with initially good graft function the zinc clearance to creatinine clearance ratio was higher during the first week after RAT than during the rest of the observation period. These findings offer no simple interpretation but suggest that, in the absence of heavy proteinuria, changes of renal zinc excretion are primarily determined by changes in the plasma concentration of ultrafiltrable zinc, which may be elevated after major operations (3). However, the contribution of a possible tubular secretion or reabsorption, or both, has not been evaluated.

After major operations and burns, urinary zinc excretion is increased and serum zinc decreased (3, 5, 8). Corticosteroid therapy has been reported to decrease serum zinc, possibly through depression of the pituitary/adrenal axis (4), but the effect of corticosteroids on the urinary zinc excretion was not published.

The measured changes in serum zinc and urinary zinc excretion after renal allotransplantation are in accordance with the changes observed after other major operations, and the influence of corticosteroid therapy on serum zinc and urinary zinc excretion seems to be of minor importance.

REFERENCES

1. Birke, G., Liljedahl, S.-O., Plantin, L.-O. & Wetterfors, J. Albumin catabolism in burns and following surgical procedures. *Acta chir. scand. 118,* 353, 1959/1960.
2. Condon, J. C. & Freeman, R. M. Zinc metabolism in renal failure. *Ann. intern. Med. 73,* 531, 1970.
3. Fell, G. S., Fleck, A., Cuthbertson, D. P., Queen, K., Morrison, C., Bessent, R. G. & Husain, S. L. Urinary zinc levels as an indication of muscle catabolism. *Lancet 1,* 280, 1973.
4. Flynn, A., Pories, W. J., Strain, W. H., Hill, O. A., Jr. & Fratianne, R. B. Rapid serum-zinc depletion associated with corticosteroid therapy. *Lancet 2,* 1169, 1971.
5. Flynn, A., Strain, W. H., Pories, W. J. & Hill, O. A., Jr. Zinc deficiency with altered adrenocortical function and its relation to delayed healing. *Lancet 1,* 789, 1973.
6. Greaves, M. W. & Skillen, A. W. Effects of long-continued ingestion of zinc sulphate in patients with venous leg ulceration. *Lancet 2,* 889, 1970.
7. Grossman, J., Yalow, A. A. & Weston, R. E. Albumin degradation and synthesis as influenced by hydrocortisone, corticotropin, and infection. *Metabolism 9,* 528, 1960.
8. Henzel, J. H., DeWeese, M. S. & Lichti, E. L. Zinc concentrations within healing wounds. Significance of postoperative zincuria on availability and requirements during tissue repair. *Arch. Surg. 100,* 349, 1970.
9. Mansouri, K., Halsted, J. A. & Gombos, E. A. Zinc, copper, magnesium, and calcium in dialyzed and non-dialyzed uremic patients. *Arch. intern. Med. 125,* 88, 1970.
10. McCance, R. A. & Widdowson, E. M. The absorption and excretion of zinc. *Biochem. J. 36,* 692, 1942.
11. Parker, M. M., Humoller, F. L. & Mahler, D. J. Determination of zinc and copper in biological material. *Clin. Chem. 13,* 40, 1967.
12. Pories, W. J., Henzel, J. H., Rob, C. G. & Strain, W. H. Acceleration of healing with zinc sulphate. *Ann. Surg. 165,* 432, 1967.
13. Prasad, A. S. & Oberleas, D. Binding of zinc to amino acids and serum proteins in vitro. *J. Lab. clin. Med. 76,* 416, 1970.
14. Sandberg, N. Time relationship between administration of cortisone and wound healing in rats. *Acta chir. scand. 127,* 446, 1964.
15. Schroeder, H. A., Nason, A. P., Tipton, I. H. & Balassa, J. J. Essential trace metals in man: zinc. Relation to environmental cadmium. *J. chron. Dis. 20,* 179, 1967.

16. Stephens, F. O., Dunphy, J. E. & Hunt, T. K. Effect of delayed administration of corticosteroids on wound contraction. *Ann. Surg. 173*, 214, 1971.
17. Vallee, B. L. Biochemistry, physiology and pathology of zinc. *Physiol. Rev.* 39, 443, 1959.
18. Walker, B. E., Dawson, J. B., Kelleker, J. & Losowsky, M. S. Plasma and urinary zinc in patients with malabsorption syndromes or hepatic cirrhosis. *Gut 14*, 943, 1973.

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