Effect of Total Parenteral Nutrition on Distribution of Zinc in Murine Tissues

R. Nezu, Y. Takagi, A. Okada, Y. Inoue,
M. Miyata and Y. Kawashima

Departments of Surgery I and Pediatric Surgery, Osaka University Medical School, Osaka 553, Japan

SUMMARY

Distribution of zinc in various tissues during total parenteral nutrition (TPN) was investigated as related to zinc deficiency. Seventy Sprague-Dawley rats were divided into two groups: Group I, fed with regular diet; Group II, fed with protein-free diet for 8 weeks. In each group, 5 rats served as control, 30 rats were further divided into two subgroups; Group Ia and IIa received TPN with 10 μmol/kg/day of zinc, and Group Ib and IIb received TPN without zinc supplementation. On the 1st, 3rd and 7th day, rats were killed and zinc concentration in plasma, red blood cells, liver, pancreas, spleen, small intestine, muscle, skin, testis, kidney, thymus and heart was measured by atomic absorption spectrophotometry. As a result, in Group I there was a significant reduction of plasma zinc concentration in Group Ib, whereas a marked increase in pancreas was noted. In Group II, there was a significant reduction of plasma and skin zinc concentration accompanied with a significant increase in total zinc content in liver and pancreas in Group IIb. These data indicate that TPN induces re-distribution of zinc in several tissues and a decrease in skin zinc concentration in Group IIb may contribute to the occurrence of skin lesion during TPN.

INTRODUCTION

Zinc deficiency during total parenteral nutrition (TPN) was first described in 1975[1,2], and is, at present, recognized as an independent entity though much remains unclear in its pathogenesis. It was usually observed during repletion, i.e., anabolic state, by TPN in severely depleted (protein-energy malnutrition: PEM) patients, supposed to be induced by an increased demand for zinc, since zinc is known to be intimately involved in the process of mitosis and protein synthesis[3]. Our previous clinical studies showed that zinc deficiency during TPN was manifested principally by characteristic skin lesion accompanied with a low plasma zinc level, while zinc concentration in red blood cells was maintained within normal range[4].

This experimental study was undertaken to investigate the re-distribution of zinc in various tissues during TPN as related to zinc deficiency.

MATERIALS AND METHODS

Seventy male Sprague-Dawley rats (Oriental Yeast, Osaka, Japan) weighing about 200g were placed in cages and acclimated to our laboratory conditions for 1 week prior to the experiment. At that time, they were divided into two groups, 35 each. Group I (normally fed rats) was continued on a commercial laboratory chow (MF; Oriental Yeast, Osaka, Japan) containing 60.5ppm of zinc ad

libitum for 1 week, and Group II (PEM rats) received protein-free diet (specially made, Oriental Yeast, Osaka, Japan) containing 37ppm of zinc ad libitum for 8 weeks. In each group, 5 rats served as control, 30 rats were further divided into two sub-groups according to TPN formula: Group Ia and IIa received TPN with 10 μmol/kg/day of zinc, whereas Group Ib and IIb received zinc-free TPN. Each rat underwent catheterization in superior vena cava with a silicone rubber catheter under ether anesthesia and received a constant infusion of 250kcal/kg/day in a metabolic cage following TPN system of Steiger[5]. No oral intake was permitted during TPN. Five rats were killed with exanguination under ether anesthesia on the 1st, 3rd and 7th day, respectively. The plasma was promptly separated. The liver, pancreas, spleen, kidney, testis, thymus, heart, small intestine, muscle and skin were removed. Plasma and red blood cells were directly diluted with redistilled water, and tissues were dissolved in nitric acid and diluted with redistilled water to desired concentrations for zinc analysis[6]. Zinc determination was made by flameless atomic absorption spectrophotometry (Hitachi 170–70, Tokyo, Japan).

Data are expressed as means ± SD. Multiple comparisons were performed after analysis of variance with the Student-Newman-Keuls test. Differences were considered to be significant when $p < 0.05$.

RESULTS

The changes in zinc concentration in various tissues during TPN for 7 days are shown in Table. There were significant changes in zinc concentration in plasma, pancreas, small intestine and skin within 7 days. Zinc concentration in plasma and skin before, on day 1, 3 and 7 of TPN in each group are shown in Figure-1. Total zinc content in liver, pancreas, spleen, testis, kidney, thymus, heart and small intestine were compensated by body weight of rats (250g for Group I and 150g for Group II, respectively). There were significant changes in total zinc content only in liver and pancreas within 7 days of TPN as shown in Figure-2.

In Group I, zinc-free TPN (Group Ib) induced significant decrease in plasma zinc concentration, whereas no significant change was observed both in zinc concentration and total zinc content in other tissues and organs. During zinc-supplemented TPN (Group Ia), zinc concentration and total zinc content in pancreas increased rapidly ($p < 0.05$ as compared to both control and Group Ib on day 3 and 7), while there was no significant change in other tissues and organs.

In Group II, zinc-free TPN (Group IIb) induced a rapid and marked decrease in plasma zinc concentration ($p < 0.05$ on day 1, 3, 7) and a gradual decrease in skin zinc concentration ($p < 0.05$ on day 3, 7), whereas total zinc content in liver and pancreas increased significantly in spite of no zinc supplementation. In Group IIa (zinc-supplemented TPN), total zinc content in liver increased significantly as much the same as Group IIb and a marked increase in zinc concentration and total zinc content in pancreas was observed, while zinc concentration in other tissues including skin showed no significant changes.

Symptoms of zinc deficiency, i.e. alopecia and diarrhea, were observed in 3 out of 5 rats in Group II

Table: Changes in Zinc Concentrations in Various Tissues during Total Parenteral Nutrition with and without Zinc Supplementation for Seven Days

	GROUP I			GROUP II				
	Control[a)]	Ia b) TPN.Zn (+)	Ib c) TPN.Zn (−)	Control[d)]	IIa e) TPN.Zn (+)	IIb f) TPN.Zn (−)		P < 0.05
PLASMA	107.2 ± 15.9	106.0 ± 13.2	84.0 ± 14.3	74.2 ± 15.3	119.8 ± 18.6	46.2 ± 9.6	μg/dl	a) vs c), d) vs e), d) vs f), e) vs f)
RED BLOOD CELLS	9.1 ± 1.9	9.6 ± 0.4	9.2 ± 1.6	10.6 ± 2.0	10.1 ± 1.8	10.3 ± 1.9	PPM	N.S.
LIVER	28.8 ± 5.8	32.8 ± 6.0	30.6 ± 8.0	20.4 ± 4.0	24.8 ± 1.5	27.5 ± 4.4	μg/g	N.S.
PANCREAS	21.3 ± 2.7	42.4 ± 10.8	26.3 ± 4.4	17.1 ± 3.3	36.9 ± 11.5	21.3 ± 3.2	μg/g	a) vs b), b) vs c), d) vs e), e) vs f)
SPLEEN	24.6 ± 1.1	20.1 ± 1.9	24.8 ± 4.4	21.6 ± 3.2	22.1 ± 0.3	23.5 ± 3.3	μg/g	N.S.
TESTIS	29.6 ± 1.9	28.4 ± 3.7	31.7 ± 5.3	26.1 ± 1.0	27.2 ± 0.9	25.1 ± 2.0	μg/g	N.S.
KIDNEY	20.8 ± 2.6	20.7 ± 1.5	20.6 ± 2.9	21.9 ± 1.2	22.9 ± 2.9	23.0 ± 3.8	μg/g	N.S.
THYMUS	20.4 ± 1.9	17.6 ± 1.1	21.4 ± 5.2	14.0 ± 2.3	19.2 ± 5.5	13.9 ± 3.2	μg/g	N.S.
HEART	18.2 ± 1.3	17.0 ± 2.1	19.6 ± 4.4	15.8 ± 1.7	15.6 ± 1.5	16.2 ± 0.8	μg/g	N.S.
SMALL INTESTINE	12.6 ± 4.0	20.7 ± 4.8	20.3 ± 5.7	19.1 ± 5.4	27.9 ± 9.2	23.1 ± 3.6	μg/g	a) vs b), a) vs c), d) vs e)
MUSCLE	16.5 ± 1.0	14.0 ± 1.6	15.3 ± 2.0	16.6 ± 3.3	15.5 ± 2.1	17.3 ± 1.1	μg/g	N.S.
SKIN	12.7 ± 2.1	11.6 ± 1.6	11.5 ± 1.4	11.9 ± 1.7	11.0 ± 1.8	8.6 ± 0.9	μg/g	d) vs f)

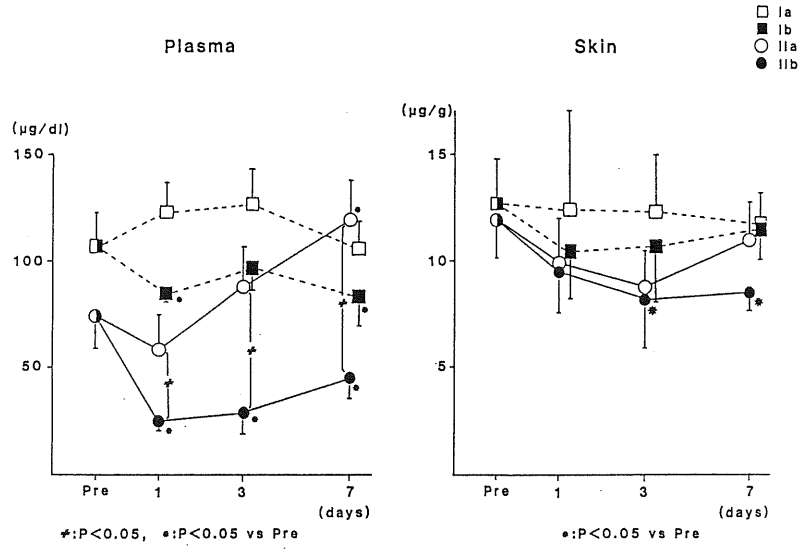

Fig. 1. Serial Changes in Plasma and Skin Zinc Concentrations.

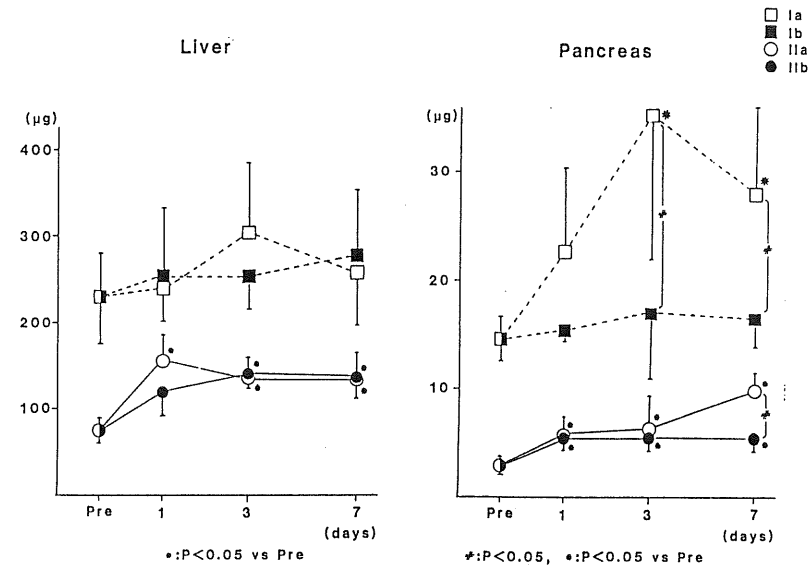

Fig. 2. Serial Changes in Total Zinc Content in Liver and Pancreas.

(PEM rats) during both zinc-free and zinc-supplemented TPN for 7 days.

DISCUSSION

Zinc is widely distributed in all tissues and is now identified as an integral constituent of more than 70 enzymes in man. Among them are carbonic anhydrase, carboxypeptidase, alkaline phosphatase,

DNA and RNA polymerases, etc.. Although its physiological functions and biochemical actions of zinc are not clearly elucidated, it seems essential for protein and amino acid metabolism, fatty acid metabolism, mitosis, and stabilization of cellular and organelle membranes[7].

Zinc deficiency during TPN is, at present, recognized as an independent entity, distinguished from chronic zinc deficiency showing growth retardation and delayed sexual maturation as described by Prasad *et al.*[8] Its pathogenesis still remains obscure, several factors may contribute. First of all, most nutrient solutions contain small amount of zinc as a contaminant, especially L-crystalline amino acid solutions. Standard TPN preparation in our institute, for example, contains only 24 μg of zinc per day for adult patient, which is less than 1/100 of the daily requirement[9]. Secondly, administration of amino acids is commonly followed by the increased losses of total body zinc[10], maybe due to the interaction of those amino acids with zinc bound to albumin, i.e., albumin-bound zinc is shifted to amino acids and this amino acids-bound zinc is freely passes the renal glomerulus and is excreted into urine. Thirdly, most of the patient indicated for TPN suffer from disease of gastrointestinal tract with malabsorption or excessive losses of intestinal fluids, and hence are likely to have a decreased store of total body zinc. Finally, there is an increased requirement for zinc in anabolic state during TPN. Restoration of body cell mass and intracellular biosynthesis in a PEM patient implies increased demand for zinc, since zinc is intimately involved in the process of mitosis and protein synthesis.

Zinc is firmly bound to the protein in tissues, thus the concentrations of zinc do not change significantly with the exceptions in several tissues during deficiency or refeeding.

In this study, there were significant changes in zinc concentration in plasma, pancreas, small intestine and skin within 7 days. The dosage of zinc supplementation, 10 μmol/kg/day, during TPN for Group Ia and IIa was determined to maintain the plasma zinc level in normally fed rats (Group Ia) by the preliminary examination.

During zinc-free TPN, the significant decrease of zinc concentration was seen only in plasma in normally fed rats (Group Ib), whereas the significant decrease was observed in plasma and skin in PEM rats (Group IIb). Serial changes in zinc concentration in plasma and skin offered a pronounced contrast in Group IIb (Figure-1); plasma zinc concentration decreased abruptly within a day and continued low, whereas skin zinc concentration decreased gradually, that indicates the mobilization of zinc from skin tissue into the other tissues or the less uptake of circulating zinc by skin tissue than by the other tissues. Zinc concentration and total zinc content in pancreas increased significantly in zinc-supplemented TPN groups that indicates the accumulation of zinc in pancreatic tissue or the stasis of pancreatic juice induced by discontinuation of oral intake. Zinc concentration in small intestine increased significantly in Group Ia, Ib and IIa, however, total zinc content in small intestine showed no significant changes. Total zinc content in liver increased significantly about twice as much as control in PEM rats irrespective of zinc supplementation; zinc-supplemented TPN induced abrupt increase, whereas zinc-free TPN induced gradual increase. These indicate that liver has preference in uptake of zinc as the most active tissue in protein synthesis during anabolic state induced by TPN in

PEM.

In conclusion, TPN induced the re-distribution of zinc in several tissues and a decrease in skin zinc concentration in PEM rats receiving zinc-free TPN may contribute to the skin lesion of zinc deficiency during TPN.

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