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Short- and long-term uses of calcium acetate do not change hair and serum zinc concentrations in hemodialysis patients

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Calcium acetate (CaAc) acutely decreases absorption of concomitantly administered zinc gluconate (Hwang *et al.*, *AJKD* 1992), but its long-term effect on zinc metabolism has not been studied. This study is intended to elucidate whether use of CaAc as phosphate binder on a daily basis affects zinc status in hemodialysis (HD) patients. Effects of CaAc on serum zinc were studied in 44 HD patients for 8 weeks (short-term). In 10 of these patients, the changes of serum and hair zinc were followed for 8 months (long-term). The daily dose of CaAc contained 25.35 mmol elemental calcium. Serum and hair zinc concentrations were measured by atomic absorptiometry. Our results were as follows: (i) in the short-term study, serum zinc concentrations did not show a significant difference compared to the baseline; (ii) in the long-term study, serum zinc concentrations showed no significant difference between different time points (11.0 ± 0.5 in the beginning, 11.9 ± 0.4 after 2 months, 11.4 ± 0.4 after 4 months and 11.3 ± 0.5 µmol/L after 8 months, $n = 10$). However, these values were all significantly lower than in the normal controls (15.7 ± 0.5 µmol/L, $n = 16$); (iii) hair zinc content was not significantly different from the baseline level (2.7 ± 0.1 in the beginning, 2.4 ± 0.1 after 2 months, 2.6 ± 0.2 after 4 months, 3.1 ± 0.1 µmol/g hair, and from that of normal controls, 2.7 ± 0.2 µmol/g hair). In conclusion, daily application of CaAc does not significantly interfere with zinc absorption and storage in HD patients. However, the comparable hair zinc content in the presence of decreased serum zinc concentrations indicates that the metabolic processing of zinc in HD patients is different from that of normal individuals.

Key words: calcium acetate; hair zinc; hemodialysis; serum zinc

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Hypozincemia in patients with chronic renal failure [1] and on maintenance hemodialysis (HD) [2, 3] is associated with abnormal taste, smell [4, 5], sexual dysfunction [6] and abnormal immune response [7, 8]. The causes of decreased serum zinc concentration in dialysis patients may be related to the redistribution of zinc metabolic pools [1], protein restriction and poor appetite [9] or impairment of intestinal absorption of zinc [10]. Medications, which decrease intestinal absorption of zinc, such as aluminium hydroxide as a phosphate binder, may induce hypozincemia in uremic patients [11, 12]. In our previous report [13], this effect was also noticed in a zinc tolerance test, and we also found that calcium acetate (CaAc), but not calcium carbonate decreased the intestinal absorption of zinc. However, these studies were all based on the findings of a small incremental increase in serum zinc concentration after one concomitant administration of phosphate binders and zinc preparation [11–13]. Whether long-term administration of phosphate binders affects the intestinal absorption of zinc from diets and subsequently changes the zinc status in HD patients is not well described. To complement the prior study of CaAc on zinc metabolism, we studied the effects of short- and long-term application of CaAc on the serum and hair zinc concentrations in maintenance HD patients.

MATERIALS AND METHODS

Short-term study

The short-term study included 44 patients on maintenance HD, with a mean age of 51.3 years and mean duration of HD of 60.2 ± 7.5 months. Informed consent was obtained from all patients before the study. Dialysis was performed 3 times a week, 4 hours each session. The dialysate calcium concentration was 3.0 meq/L and the dialyser used in this study was made of ethylene vinylalcohol copolymer (KF-201, Kuraray, Laboratories, Japan. After discontinuing all phosphate binders for 1 week as the washout period, CaAc (Ace-Cal®, 667 mg/Tab, =4.2 mmol (169 mg) elemental calcium per tablet) was given to each patient at each meal with a daily dose of 25.35 mmol (1014 mg) elemental calcium for 8 weeks. The dosage of active vitamin D was not changed during the study period in any patient receiving this medication. Multivitamin supplements in each patient did not contain zinc. The daily protein intake of dialysis patients was around 1.0–1.2 g/kg/day. Blood was drawn for measurements of calcium and phosphate every 2 weeks. Serum zinc was measured every 4 weeks. The dosage of CaAc was adjusted according to serum calcium and phosphate levels to avoid hypercalcemia.

Long-term study

Since serum zinc concentration might not parallel body zinc storage, we further studied the long-term effect of CaAc on hair zinc concentration in addition to the serum levels in 10 patients. Since control of all conditions, including medications and diet, for a long-term study is not possible with every patient, we restricted each patient to particular groups in order to avoid bias resulting from lack of compliance. These 10 patients were selected from the group of 44 after evaluation of drug compliance and were alleged to have good compliance. Daily doses of CaAc with each meal were given for 8 months. These 10 patients had a mean age of 50.4 years and a mean duration of dialysis of 56.3 ± 18.3 months. The HD schedule and medications other than CaAc were unchanged, and the diet habits in these 10 patients did not change much during the study period. Zinc preparation was not given. No concurrent major illness occurred during this period. Serum zinc, ionized calcium, phosphate and hair zinc concentrations were measured at baseline and at the end of the 2nd, 4th and 8th months. Serum and hair zinc concentrations were determined in 16 medical staff members with a mean age of 40.8 years, who served as references.

Measurements of serum and hair zinc

Blood samples were collected into a vacuum glass tube free of zinc and anticoagulant, centrifuged at 3000 g for 10 min at 4°C. Serum was stored in acid-treated polystyrene tubes at −20°C until assay. Serum zinc was measured by atomic absorption spectrophotometry (Perkin-Elmer, Norwalk, CT, Model 503) as previously described [13]. For hair zinc measurement, 1 g of the proximal part of the hair shaft over the occipital region was obtained from each individual and was washed with distilled water and acetone. After drying, 0.1–0.13 g of the treated samples were acidified with pure nitric acid and heated at 100°C for 1 h. The dissolved aliquots were then assayed for zinc by atomic absorptiometry. The sensitivity of the zinc assay was

1 μg/L. The intra-assay coefficients of variance for serum and hair zinc were 2.1% and 1.0%, respectively. The inter-assay coefficient of variance for hair zinc was 5.4%.

Statistics

The data are expressed as mean ± SEM. One-way repeated measures analysis of variance was used to check the difference for each item. The comparison between groups was done using Student's unpaired *t*-test. The difference was considered statistically significant when the p-value was <0.05.

RESULTS

Short-term study

The serum zinc, ionized calcium and phosphate concentrations of the 44 patients at baseline, week 4 and week 8 after CaAc administration were analysed. Serum phosphate decreased significantly after CaAc treatment (baseline: 2.1 ± 0.02; week 4 : 1.6 ± 0.02*; week 8 : 1.7 ± 0.02* mmol/L, $p<0.05$), which is consistent with the hypophosphatemic effect of CaAc, while serum ionized calcium was also increased (baseline: 1.2 ± 0.02; week 4: 1.4 ± 0.02*; week 8 : 1.3 ± 0.02* mmol/L, $p<0.05$). The serum zinc in the 44 patients receiving CaAc was not significantly different at week 4 or week 8 of CaAc treatment compared to the baseline levels (baseline: 11.3 ± 0.3; week 4: 10.5 ± 0.2; week 8: 11.1 ± 0.3 μmol/L).

Long-term study

The serum zinc, ionized calcium, phosphate and the hair zinc concentrations in 10 HD patients at baseline and 2, 4 and 8 months after CaAc administration are shown in Table I. The respective serum zinc at each time point showed no significant difference from baseline. Hair zinc at any time point was not significantly different from that of baseline. With the serum zinc at every time point significantly lower (all $p<0.05$) compared to that of normal controls, the hair zinc content at any time point was not significantly different from that of the normal controls. The comparisons of baseline, 8-month serum and hair zinc to that of normal controls are shown in Fig. 1. Both serum calcium and

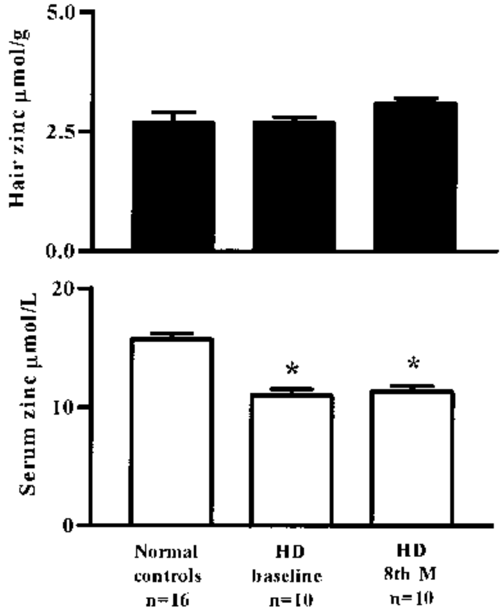

FIG. 1. Serum and hair zinc in 10 maintenance hemodialysis (HD) patients and 16 normal controls. Significant decrease of serum zinc concentration in hemodialysis patients at baseline and 8 months after calcium acetate treatment compared to normal controls, but no difference in hair zinc content compared to normal controls. Date are expressed as mean ± SEM. *$p<0.05$ compared to normal controls by Student's *t*-test.

TABLE I. Serial changes of serum and hair zinc (Zn), ionized calcium (iCa) and phosphate (P) in 10 hemodialysis patients receiving calcium acetate for 8 months.

	Baseline	2nd month	4th month	8th month
Hair Zn (μmol/g)	2.7 ± 0.1	2.4 ± 0.1	2.6 ± 0.2	3.1 ± 0.2
Serum Zn (μmol/L)	11.1 ± 0.5	11.9 ± 0.4	11.4 ± 0.4	11.3 ± 0.05
Serum iCa (mmol/L)	1.2 ± 0.02	1.4 ± 0.02*	1.3 ± 0.02	1.3 ± 0.04
Serum P (μmol/L)	2.0 ± 0.2	1.7 ± 0.1*	1.8 ± 0.1	1.6 ± 0.1*

Date are expressed as means ± SEM. *$p<0.05$ compared to the baseline value of each item.

phosphate were significantly different from the baseline levels during the CaAc treatment period (Table I).

DISCUSSION

Decreased serum zinc concentration is common in both non-dialysed or dialysed uremic patients [1 – 3]. This may be caused by poor appetite and protein malnutrition [9], and results directly from decreased intestinal absorption of zinc [10]. Medications prescribed for dialysed uremic patients, such as vitamin D and phosphate binders, may influence intestinal zinc absorption. Use of vitamin D was reported to increase intestinal zinc absorption and enhance positive zinc balance [14]. In addition, the widely used phosphate binders in HD patients may also influence intestinal zinc absorption. In the study of Abu-Hamdan *et al.* [11] and our prior studies [12], concomitant administration of phosphate binders (aluminium hydroxide or CaAc) significantly decreased the zinc absorption in HD patients. Such an effect was not found in the study using calcium carbonate [13].

However, in these studies, the intestinal absorption of zinc was evaluated using a zinc tolerance test, an indirect method reflecting immediate intestinal zinc absorption and the influence of phosphate binders on zinc absorption [15]. This test is not applicable to HD patients. Almost all of them took the prescribed phosphate binders on a daily basis, with every meal or immediately after meals. Thus, the absorption of zinc from food may not be the same as that in the zinc tolerance test. In this study, we tried to keep the medication and diet habits of HD patients constant by frequent inquiry. In addition, our observation up to 8 months not only provided data to compare with the results of immediate and short-term effects, but also avoided the bias possibly caused by strict requests on food compliance characteristic of short-term study.

Although CaAc was found to decrease the intestinal absorption of zinc in HD patients according to a zinc tolerance test [13], the serum zinc levels were not significantly decreased compared to the baseline in this study, neither short- nor long-term. This suggested that HD patients taking CaAc as a phosphate binder would not have their serum zinc levels affected. The differences in the time of evaluation of serum zinc concentrations (one was immediate intestinal absorption effect, but the other was based on daily living conditions) could explain why there were such differences in results. Our result was also different from those of Gilli *et al.* [16]. In that report, plasma zinc concentrations were found to be significantly decreased in HD patients after the use of calcium carbonate as a phosphate binder for 6 months, whereas they were unchanged after the use of aluminium hydroxide. The effect of calcium carbonate on immediate intestinal absorption of zinc was not compromised by concomitant administration of calcium carbonate in our previous study [13]. The reason for such different results in the effects of calcium carbonate on serum zinc concentration is not clear. However, in this study we did not evaluate the effect of calcium carbonate in long-term observation.

Other conditions that influenced zinc metabolism in dialysis patients included the treatment of anaemia with erythropoietin, which has been reported to increase serum zinc in HD patients [17]. In our study, the dosage of erythropoietin was not changed during the 8-month study period; thus, this factor might not be relevant. Dietary stuff containing phytate and large amounts of calcium decrease zinc absorption; formation of a calcium, zinc and phytate complex is thought to be the cause [16]. CaAc also contains large amounts of calcium and its phosphate-binding capacity is more efficient than that of calcium carbonate. Therefore, formation of complexes does not explain the results of our study. Another explanation could be the different food constituents and methods of cooking between eastern and western societies. Strict monitoring of the diet is definitely helpful, but not practical in such a study. Instead, patients' diet habits were monitored by frequent communication, inquiry and avoidance of high-zinc content food.

It has been clearly shown that plasma zinc is decreased in dialysis patients [1, 2, 18], but reports on the level of hair zinc are inconsistent. Both no difference from normal controls [1, 18] and decreased concentrations in dialysis patients [2, 4] have been reported. Hair zinc content has been used to reflect the body storage of zinc [2, 18]. In our study, we also considered hair zinc to reflect the change of zinc storage in response to CaAc application. We found decreased serum zinc, but no difference in hair zinc in HD patients compared to normal controls. This suggests that the storage of zinc in HD patients does not change after CaAc treatment. Studies of serum and hair zinc concentrations in normal individuals and in uremic patients have yielded controversial results in the literature. Immediate absorption, serum concentration equilibrium and dynamics between serum pool and storage sites on the basis of immediate, short- and long-term study can vary greatly. Our study is not wide enough in scope to answer such a complicated question, but the consistent low serum zinc concentrations in dialysis patients, but normal hair zinc content, indicated that zinc metabolism was altered in this group of patients. The changes in sense of taste, smell, sexual function or immune response which have been reported in dialysis patients with zinc deficiency could also be influenced by other factors in addition to zinc status. These parameters were also beyond the scope of this study.

In summary, despite a decreased intestinal zinc absorption demonstrated in the study using CaAc by the zinc tolerance test, long-term application of CaAc in HD patients did not change their hair zinc levels. The decrease in serum zinc, but not hair zinc concentrations is consistent in HD patients, which may indicate an altered metabolic process for zinc in dialysis patients.

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