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Original article

Essential trace element status and clinical outcomes in long-term dialysis patients: A two-year prospective observational cohort study

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SUMMARY

Background & aims: Essential trace elements are involved in many biological processes for normal cell function including immunological defense against oxidation and infection. Deficiency of these elements generally leads to illness or even death in the general population. Therefore, we investigated the predictive values of trace element status on clinical outcomes in dialysis patients, who are more prone to trace element deficiency.
Methods: We enrolled 111 prevalent patients on maintenance dialysis from a Taipei tertiary-care referral hospital and measured serum levels of selenium, copper, and zinc. Patients were followed for 2 years or until death or withdrawal.
Results: Multivariate Cox regression analysis indicated that patients with diabetes mellitus (HR, 2.162 [95% CI, 1.105–4.232], $p = 0.024$), prior stroke (HR, 3.876 [95% CI, 1.136–13.221], $p = 0.030$), and zinc deficiency (HR, 0.979 [95% CI, 0.966–0.992], $p = 0.002$) were more likely to be hospitalized for infectious diseases. Furthermore, beyond traditional risk factors, such as old age and hypoalbuminemia, multivariate Cox regression also indicated that lower serum level of zinc independently predicts overall mortality (HR, 0.973 [95% CI, 0.948–0.999], $p = 0.046$).
Conclusions: In long-term dialysis patients, the serum level of zinc was an independent predictor of future hospitalization due to infectious diseases and of overall mortality.

1. Introduction

Although uremic patients undergoing long-term dialysis may accumulate deleterious toxic trace elements, such as arsenic, mercury, lead and cadmium due to the use of contaminated dialysis fluid,[1] essential trace element deficiencies such as selenium (Se) and zinc (Zn) are prevalent among dialysis patients.[2–4] Deficiency in trace elements is known to have adverse health effects, and the biological impact in patients with renal insufficiency is even higher than in the general population.

Essential trace element status was independently related to immune status, inflammation, oxidative damage, lymphocyte function, and granulocyte motility.[5–14] For example, at the molecular level, Zn is an important co-factor for diverse enzymes, peptides, transcriptional factors, and cytokines that are involved in various aspects of normal immune responses.[6] Meanwhile, Zn is essential for one of the most important free radical scavengers, the copper zinc form of superoxide dismutase (CuZuSOD, SOD1). Furthermore, a previous study showed that Zn supplementation decreases the serum level of C-reactive protein (CRP) in dialysis patients.[15] Trace elements are essential for the maintenance of normal immune system function, so patients with essential trace element deficiencies are expected to be more susceptible to infectious diseases and have worse prognoses. However, very few studies have examined the effect of these deficiencies on clinical outcomes.[1–3,16]

Dialysis patients are at risk for essential trace element deficiencies and infectious diseases, so we postulated that the poor

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immune function of dialysis patients may be partly related to their essential trace element deficiencies. The aim of this study was to examine whether essential trace element deficiencies are associated with future infectious diseases or mortality in end-stage renal disease (ESRD) patients undergoing long-term dialysis.

2. Patients and methods

2.1. Study protocol and subjects

From July 2008 to June 2010, we conducted a prospective observational cohort study at Taipei Veterans General Hospital, a tertiary-care referral hospital. Each subject provided written informed consent, and the Institutional Review Board of this institution approved the study. All patients were at least 18 years of age, had ESRD, and were on maintenance hemodialysis (HD) or peritoneal dialysis (PD) for at least 6 months. We excluded patients who refused to provide consent, and who did not agree to the blood test for trace elements after an 8-h fasting period. A total of 43 HD patients and 68 PD patients were enrolled.

At the study entry, all patients underwent measurement of serum essential trace elements, including Se, copper (Cu), and Zn. Demographic features and clinical parameters, including age, gender, duration of dialysis, body weight index, comorbidities, nutritional supplements, medications, serum biochemical data, and blood cell counts were recorded. The indices of smoking and alcohol consumption were coded as never (0), quit (1), less than once weekly (2), more than once weekly (3), and at least once daily (4). The index of the exposure history of heavy metal chemicals were coded as never (0), less than once weekly (1), more than once weekly (2). The indices of herbal drug use and vitamin supplement were coded as at least once daily (1), more than once weekly (2), less than once weekly (3), and never (4).

2.2. Healthy subjects

We also checked the serum levels of essential trace elements in 67 healthy subjects with normal renal function. Mean age was 36 years and 64% of patients were male. A total of 1 patient (1.5%) had diabetes mellitus and 7 patients (10.4%) had hypertension among healthy subjects.

2.3. Dialysis procedures

HD was performed three times weekly (4 h per session) using 1.8-m^2 surface area dialyzers with bicarbonate-based dialysates with calcium at a concentration of 2.5–3.0 mEq/L. PD was provided as continuous ambulatory PD or automated PD. All patients were treated with recombinant human erythropoietin, with a target hematocrit level of 30–36%. Kt/V of HD patients was 1.67 ± 0.24, and Kt/V of PD patients was 2.17 ± 0.40.

2.4. Measurements of serum trace elements

Fasting venous blood specimens were drawn before the midweek HD session and collected into no additive Vacutainer blood-collecting tubes (Becton–Dickinson, Franklin Lakes, New Jersey, USA) according to standard hospital guidelines for venipuncture and sample collection. The serum separator tube specimens were allowed to clot and then were centrifuged for 5 min at 5000 rpm to separate the serum. Serum samples were stored at the refrigerator (2–8 °C). All samples were well-mixed at room temperature prior to analysis. Each 0.4 mL serum sample was added with 0.4 mL internal standard and 4 mL 2% nitric acid. The mixture was vortex-mixed and centrifuged for 5 min at 5000 rpm. Serum levels of Se, Cu, and Zn were determined with an Elan 6100 DRC Plus inductively coupled plasma mass spectrometry (Perkin Elmer, Waltham, USA). All the calibrators and samples were placed in the autosampler tray. Yttrium was used as internal standard.

2.5. Clinical outcomes

After baseline assessments, all patients were followed for 2 years or until death. Patients who received kidney transplantation were censored at the time of transplantation. Clinical outcomes evaluated were the first episode of infection requiring hospitalization and overall mortality. For patients with multiple hospitalizations for infection, survival analysis in relation to hospitalization for infection was limited to the first hospitalization during the follow-up period. The diagnosis of infectious diseases and the causes of death were determined by the attending physicians who had no knowledge of the baseline serum Zn levels. In case of death that occurred out of our hospital, family members were interviewed by telephone to ascertain the cause and time of death.

2.6. Statistical analysis

Chi-square analysis or Fisher's exact test was used for comparison of categorical variables as appropriate. Continuous variables were compared by Student's *t*-test. Values of the continuous variables are presented as mean and standard deviation, unless otherwise specified. The Cox proportional hazards model was used to determine the significance of variables in predicting the primary end-point. Variables associated with clinical outcomes in univariate Cox regression analysis with p value less than 0.10 were used for multivariate Cox regression analysis. Kaplan–Meier analysis was used to assess the difference between patients with serum Zn levels greater than the median level (72.2 μg/dL) and those with serum Zn levels less than 72.2 μg/dL in reaching the primary end-point. This comparison was performed by the Log-rank test. The correlation between serum Zn and serum albumin was analyzed using linear regression analysis. Because serum levels of albumin and Zn both reflects nutritional status, we categorized our patients into 4 groups according to their median serum levels of albumin and Zn in order to further analyze the role of these 2 parameters in the clinical outcomes of dialysis patients. We used Kaplan–Meier analysis to assess survival differences between these 4 groups. SPSS version 15.0 for Windows (SPSS Inc., Chicago, Illinois, USA) was used for all statistical analyses. All probabilities were two-tailed and a p value of less than 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics of study subjects

Table 1 shows the baseline characteristics of the 111 patients who were followed for 2 years. Mean age was 58 years, 29% of patients were male, and mean duration on dialysis was 6.5 years. The mean serum essential trace element levels were 7.07 ± 2.23 μg/dL (range, 1.48–14.60 μg/dL) for Se, 83.85 ± 38.14 μg/dL (range, 18.59–205.26 μg/dL) for Cu, and 79.26 ± 33.16 μg/dL (range, 16.83–225.71 μg/dL) for Zn, which showed a low normal value as compared to our institutional reference ranges (7–19 μg/dL for Se, 57–125 μg/dL (male) and 61–130 μg/dL (female) for Cu, and 61–130 μg/dL for Zn, respectively). A total of 31 patients (28%) had diabetes mellitus, 82 patients (74%) had hypertension, 26 patients (23%) had hyperlipidemia, 19 patients (17%) had cardiovascular diseases, and 4 patients (4%) had history of stroke. Compared to patients with serum Zn above the median value of 72.2 μg/dL, those with serum Zn below the median were more likely to have diabetes