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Mortality of combined serum phosphorus and parathyroid hormone concentrations and their changes over time in hemodialysis patients

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ABSTRACT

Background: Mineral and bone disorder (MBD) is common and associated with mortality in patients with chronic kidney disease (CKD) Given that disarrays in serum phosphorus (P) and parathyroid hormone (PTH) levels and their changes over time are closely interrelated, modeling mortality–predictability of their combinations may help improve CKD patient management.
Methods: A historical cohort study was undertaken to evaluate the joint effect of serum P and PTH levels on mortality in 107,299 chronic hemodialysis (HD) patients. Changes in serum P and PTH levels over 6 months, in particular discordant changes, were also modeled with mortality.
Results: HD patients were 64 ± 15 (mean ± SD) years old and included 45% women, 33% African-American, and 59% diabetic. Compared with serum P level ≥7.0 mg/dL and PTH level ≥600 pg/mL, adjusted hazard ratio (HR) tended to be lowest in patients with serum P level of 3.5–<5.5 mg/dL combined with PTH level of 150–<300 pg/mL (HR 0.64, 95% confidence interval 0.61–0.67). A change over time in serum P level towards the 3.5–<5.5 mg/dL range from higher or lower ranges was associated with a decreased mortality, whereas only change in PTH level from <150 pg/mL to 150–<300 pg/mL range was associated with a lower risk of mortality. Upon discordant changes of PTH and P, i.e., decrease in one of the two measures while the other increased, no change in mortality risk was observed.
Conclusion: In CKD-MBD management, patent survival is the greatest with controlling both serum P and PTH levels in balance. Tailoring an individualized treatment strategy in CKD-MBD may benefit patients. Further studies are needed.

Introduction

Abnormalities in serum calcium, phosphorus (P), and parathyroid hormone (PTH) levels are common in patients with chronic kidney disease (CKD). These biochemical changes together with elevation of fibroblast growth factor-23 (FGF-23) and abnormalities in vitamin D metabolism constitute a systemic syndrome known as chronic kidney disease–mineral and bone disorder (CKD-MBD). Observational studies have found associations of serum phosphorus (P) and parathyroid hormone (PTH) with mortality in patients with CKD [1,2] and in patients on maintenance dialysis [3–11]. Although no conclusive clinical trials have been conducted yet, hyperphosphatemia and secondary hyperparathyroidism have been recommended as major targets to treat CKD-MBD [12,13]. Since serum P and PTH levels are physiologically interrelated, [14,15] it may be plausible that both parameters be considered simultaneously in risk stratification, planning and adjusting treatments for CKD-MBD. In this respect, a model combining serum P with PTH level as a "bivariate" predictor may fit a survival model better than a model that treats each parameter separately. In addition to static levels of serum P and PTH, dynamic change over time may be also important. However, effect of changes in serum P and PTH levels on mortality has been insufficiently evaluated, especially in discordant (i.e. increase in serum P level but decrease in PTH level or vice versa) changes [16].

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We hypothesized that concurrent preferable levels of serum P and PTH are associated with better survival in hemodialysis (HD) patients, and that changes in serum P and PTH levels to a preferable level would also be associated with lower mortality. Evaluation for discordant changes may give insight about situations faced during treatment of CKD-MBD in clinical practice. We evaluated our hypothesis with a large and contemporary cohort of HD patients.

Materials and methods

Patients

We retrospectively examined data from all patients receiving HD treatment from July 1, 2001, to June 30, 2006 in a large dialysis care organization in the United States (DaVita Inc.). As a dialysis population is a dynamic cohort with a high turnover rate, a non-concurrent cohort was formed. Prevalent patients as of July 1, 2001 and incident patients from July 1, 2001 to June 30, 2006 were included, which has been described in our previous studies [17,18]. The first (baseline) quarter for each patient was the calendar quarter in which the patient's dialysis duration was longer than 90 days. Patients were considered to be treated with HD if they were on the therapy at entry into cohort. During the cohort period, a total of 164,789 patients received dialysis treatment, among whom 130,087 had both serum P and intact PTH measures. After excluding 22,788 patients on PD or without data for dialysis modality at cohort entry, 107,299 HD patients were selected for the study. There was no significant difference in demographics between included and excluded HD patients. Follow-up time began on the date of entry into the cohort. Date and cause of death were recorded. Patients were censored at time of renal transplantation, departure from DaVita facilities, or end of the study period (June 30, 2006). The study was approved by the relevant Institutional Review Committees with exemption for a written consent.

Demographic and clinical measures

Information on dialysis modality and treatment, body weights, laboratory values, and intravenous medications were obtained from DaVita Inc. databases. These data were merged with data from the US Renal Data System (USRDS) to obtain information on date of first dialysis treatment, race/ethnicity, marital status, insurance, and co-morbid conditions. The following comorbid conditions were considered: diabetes mellitus, hypertension, ischemic heart disease, congestive heart failure, cerebrovascular accident, peripheral vascular disease, chronic obstructive pulmonary disease, malignancy, non-ambulatory state, and current smoking. Information on comorbidities was collected at the start of dialysis based on the Medical Evidence Report for ESRD (Form 2728). Dialysis duration was defined as the time between the first day of dialysis treatment and the first day that the patient entered the cohort.

Laboratory values

Most blood samples were collected by uniform techniques in all dialysis clinics at the beginning of HD treatment. All samples were transported within 24 h to a single laboratory center (DaVita Laboratory, Deland, FL), and then were measured by automated and standardized methods. Serum intact PTH level was measured by immunoradiometric assay utilizing a polyclonal 1–84 PTH Label Antibody, labeled with ^{125}I-, with a tendency to bind in the N terminal region on 1–84 PTH, and a Capture Antibody, polyclonal goat anti-PTH (39–84) fixed to the tubes, with a tendency to bind in the C terminal region of 1–84 PTH (Nichols, San Juan Capistrano, CA, USA). Precision inter- and intra-assay coefficient of variation was evaluated by performing 20 different assays on 3 EDTA plasma samples. The mean coefficient of variation for inter-assays was 4.68% and for intra-assays 2.47%. Serum P, calcium, urea, albumin, bicarbonate and total iron binding capacity were measured monthly. Serum intact PTH and ferritin were measured at least quarterly. Hemoglobin was measured weekly to bi-weekly in most patients. Delivered dialysis dose was estimated by single-pooled Kt/V using the urea kinetic model. Normalized protein nitrogen appearance (nPNA) was used as indicator of dietary protein intake. The 3-month-averaged values during the patient's first eligible quarter were used as baseline values in order to attenuate an effect of short-term variation in laboratory measurements.

Composite ranking score analysis

Changes in serum P level (Δ P) and intact PTH level (Δ intact PTH) were calculated as a mean of third quarter measured values *minus* a mean of first quarter measured values in each patient (i.e. change during the first 6 months after entry into the cohort). We chose the first 6-month interval because serum P and PTH levels tend to be high before start of maintenance dialysis treatment and then are gradually controlled usually within 6 months in incident HD patients. Eligible patients were ranked with respect to Δ P and Δ intact PTH. We ranked these change values as −100th to 0th percentiles for declines and 0th to +100th percentiles for rises. We then subtracted these two change scores (i.e. rank of Δ P *minus* rank of Δ intact PTH) for each patient to create composite ranking scores (a number between −200 to +200 for each subject). The difference reflects discordant changes; with a decrease in serum P level but an increase in intact PTH level predominating below −100, while with an increase in serum P level but a decrease in intact PTH level predominating above 100. Using composite ranking scores enabled us to distinguish which lab measurement predominated in a discordant change. Examples using derived composite ranking score have been described in our previous papers [19,20].

Statistical methods

Data were summarized using proportions, means (±standard deviation, SD) and medians (interquartile range, IQR) as appropriate. We divided serum P levels a priori into 4 categories (<3.5, 3.5 to <5.5, 5.5 to <7.0 and ≥7.0 mg/dL) and intact PTH levels into 4 categories (<150, 150 to <300, 300 to <600, and ≥600 pg/mL) based on Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines for mineral bone disease because patients in our cohort were enrolled from 2001 to 2006 and were treated according to this guideline [12]. Patients were then divided into 16 groups according to their serum P and intact PTH levels (4 × 4 groups). Patients with serum P level of ≥7.0 mg/dL and intact PTH level of ≥600 pg/mL were considered as the reference group, for which we expected the worst outcome. For analysis of change in serum P level, we stratified patients based on their baseline values (<3.5, 3.5 to <5.5 and ≥5.5 mg/dL), and then further divided these groups into 3 strata based on their 3rd quarter serum P levels (<3.5, 3.5 to <5.5 and ≥5.5 mg/dL). Patients who did not change the category of serum P level between baseline and 3rd quarter were treated as the reference group. We similarly analyzed change in serum intact PTH level using 3 categories (<150, 150 to <300 and ≥300 pg/mL). The method for calculating composite ranking score is mentioned above. Survival analysis was performed by fitting Cox proportional hazard models with all-cause mortality as the outcome. The predictors were baseline serum P and intact PTH levels (4 × 4 groups), change in serum P level (3 × 3 groups), change in serum intact PTH level (3 × 3 groups) and composite ranking score. For composite ranking score analysis, Cox regression with restricted cubic splines was used. The assumption of proportional hazard was assessed by log–log plots and Schoenfeld residuals after fitting models.

For each analysis, 3 levels of multivariable adjustment were examined: 1) an unadjusted model that included only the main predictor variable(s) and calendar quarter of entry; 2) case-mix adjusted models that additionally included age, gender, race/ethnicity, comorbidities, primary insurance, marital status, dialysis duration, vascular access type, single-pool Kt/V and serum total calcium level as covariates;