Risk Factors and Risk for Mortality of Mild Hypoparathyroidism in Hemodialysis Patients

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• Relative hypoparathyroidism (parathyroid hormone [PTH] ≤ 200 pg/mL) is prevalent in hemodialysis (HD) patients, with unknown pathogenesis and prognosis. Thus, to clarify risk factors and prognosis of time-dependent relative hypoparathyroidism in HD patients, a retrospective cohort study was performed for 126 HD patients with four or more PTH determinations and no previous total or subtotal parathyroidectomy. Values for intact PTH, ionized calcium, phosphate, magnesium, albumin, creatinine, urea reduction ratio (URR), glucose, hemoglobin A_{1c} (HbA_{1c}), aluminum, and $1,25(OH)_2D$ were obtained at enrollment and at some time during follow-up. The prevalence of relative hypoparathyroidism at entry was 76 of 126 patients (60.3%). Univariate analysis showed that patients with hypoparathyroidism were older, more likely to have diabetes, and had greater ionized calcium levels and lower phosphate, albumin, blood urea nitrogen (BUN), and creatinine levels. Patients with diabetes were older and had a shorter duration of dialysis therapy and lower PTH, phosphate, albumin, BUN, and creatinine levels and URRs. Conversely, multivariate analysis showed that PTH levels at entry were associated directly with creatinine levels and inversely with age and ionized calcium levels (but not diabetes). During follow-up, PTH levels fluctuated concomitantly with ionized calcium and phosphate levels over time in all patients. Time-dependent PTH levels were associated directly with duration of dialysis therapy and use of vitamin D and phosphate and albumin levels, but inversely with age and ionized calcium and magnesium levels (but not glucose or HbA_{1c} levels). Interestingly, time-dependent PTH levels were independently associated with survival after adjusting for traditional risk factors (diabetes, age, albumin and creatinine levels, and URR) and duration of dialysis therapy. We conclude that in HD patients, relative hypoparathyroidism was not associated with diabetes per se. Time-dependent PTH levels were associated with age, duration of dialysis, and levels of ionized calcium, phosphate, albumin, and magnesium. Moreover, relative hypoparathyroidism at entry and lower time-dependent PTH levels predict mortality.

INDEX WORDS: Hemodialysis (HD); mortality; hypoparathyroidism; retrospective cohort study.

THE PREVALENCE OF relative hypoparathyroidism is increasing to as high as 64.4% among hemodialysis (HD) patients.[1] Its clinical significance is not known, although it has been associated with adynamic bone disease.[2] Adynamic bone disease has emerged as the most common form of renal osteodystrophy in dialysis patients.[2] Conversely, secondary hyperparathyroidism has been studied thoroughly and is considered detrimental to uremic patients,[3] although it has never been independently associated with mortality in dialysis patients.

Several researchers have studied risk factors for relative hypoparathyroidism in HD patients.[1,4-7] Unfortunately, all used univariate analyses in cross-sectional studies and failed to account for many factors that affect parathyroid hormone (PTH) levels.[8] In addition, although multiple regression was used in a relevant study,[5] it was only a cross-sectional case-control study and therefore failed to detect changes over time in individual patients. Also, cross-sectional studies have inherent disadvantages, whereas the study of events in time and an appreciation of the picture of health and disease over time are fundamental to biomedical research and public health surveillance.[9,10] Moreover, the natural history of uremic relative hypoparathyroidism remains unknown.

Therefore, in a retrospective cohort study of HD patients, we attempted to determine: (1) risk factors for enrollment and time-dependent relative hypoparathyroidism, (2) whether relative hypoparathyroidism was a fixed or dynamic state during serial follow-ups, and (3) whether time-dependent PTH levels were associated with mortality.

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METHODS

We reviewed records of 212 maintenance HD patients in April 2000. Patients were included if they met the following criteria: (1) older than 18 years, (2) four or more intact PTH measurements available after April 1990, (3) alive for 1 year or longer, (4) never underwent total or subtotal parathyroidectomy, and (5) never administered pulse intravenous high-dose active vitamin D treatment. Criteria as listed excluded 86 patients, including 14 patients with total or subtotal parathyroidectomy, 18 patients administered pulse intravenous high-dose active vitamin D treatment, 17 patients who survived less than 1 year, 2 patients younger than 18 years, and 35 patients with fewer than four intact PTH determinations after April 1990. Accordingly, 40 patients with diabetes and 86 patients without diabetes were recruited. Because serum PTH level was the main outcome, we limited the study to patients with at least four PTH measurements, the minimum number of observations required for a meaningful statistical assessment.

The study protocol was approved by the institutional review board. Participants underwent HD three times weekly using hollow-fiber dialyzers and bicarbonate dialysates containing calcium and magnesium at concentrations of 2.5 to 3.5 and 1.0 mEq/L, respectively. Patients were administered calcium carbonate (n = 112) and aluminum hydroxide (n = 36) as phosphate binders. Note that some patients (n = 24) were administered a combination of calcium carbonate and aluminum hydroxide. Oral active vitamin D (1,α-(OH)-vitamin D_3; Chugai Co, Tokyo, Japan) was administered to 11 patients at dosages of 0.25 to 1.0 μg/d. According to the regulations of Health Insurance Agencies, recombinant human erythropoietin (rHuEPO) was administered (0 to 20,000 U/mon intravenously or subcutaneously) to keep hemoglobin at a target level of 10 g/dL since July 1993. Thus, rHuEPO dosage was coded as 0 for data before July 1993.

Diabetes mellitus was diagnosed based on one of the following criteria: (1) history of physician-diagnosed diabetes, (2) history of insulin therapy, (3) history of oral hypoglycemic therapy, or (4) history of fasting glucose level of 126 mg/dL or greater or postprandial glucose level of 200 mg/dL or greater on at least two occasions. For patients with diabetes, fasting plasma glucose levels were used as a measure of short-term glycemic control, whereas hemoglobin A_{1c} (HbA_{1c}) levels were used as an index of long-term glycemic control. Blood urea nitrogen (BUN), creatinine, ionized calcium, phosphate, albumin, and glucose (for patients with diabetes) were measured every month, whereas PTH was measured every 3 months. Magnesium and aluminum were measured every 6 months.

Cross-Sectional (enrollment) Data and Retrospective Cohort Study

Data for 126 patients (55 men, 71 women; age, 53.1 $\pm$ 1.24 years; HD duration, 16 $\pm$ 1.9 months) who first met inclusion criteria were enrolled onto a cross-sectional study. These patients were followed up for serial levels of PTH, ionized calcium, phosphate, and the other variables in a retrospective observational cohort study.

Laboratory Measurements

Predialysis fasting samples were measured. Serum intact PTH was measured using the Allegro Immunoradiometric Assay (Nichols Institute, San Juan Capistrano, CA; reference range, 10 to 65 pg/mL) with a sensitivity of 1.8 pg/mL and intra-assay and interassay coefficients of variation of 5.6% and 7.7%, respectively.[11] Hypoparathyroidism was arbitrarily defined as a PTH level of 200 pg/mL or less based on two considerations. First, recent consensus suggests that PTH levels should be kept at 100 to 200 pg/mL to maintain normal skeletal bone turnover.[12] Second, a recent study showed that absolute (PTH $<$ 65 pg/mL), but not relative (PTH, 65 to 200 pg/mL), hypoparathyroidism is associated with mortality[13]; therefore, we designed the study to establish the relationship between PTH levels and mortality.

Serum BUN, creatinine, phosphate (reference range, 2.5 to 4.5 mg/dL), plasma glucose, and complete blood count were measured using a routine autoanalyzer (Hitachi 736-40, Tokyo, Japan). Ionized calcium was measured using an ionized calcium analyzer (reference range, 4.2 $\sim$ 5.3 mg/dL; Nova Biomedical, Waltham, MA). Serum magnesium was measured using the atomic absorption method (reference range, 1.7 $\sim$ 2.3 mEq/L; Perkin-Elmer Corp, Shelton, CT). HbA_{1c} (reference range, 4.3% to 6.1%) was tested every 4 months in patients with diabetes by means of the high-performance liquid chromatography (HPLC) method (Hemoglobin A_{1c} by HPLC; Bio-Rad Co, Hercules, CA). Serum aluminum (reference range, $<$10 μg/L) was measured by flameless atomic absorption spectrophotometry, whereas serum $1,25(OH)_2D$ was measured using a radioreceptor assay kit for a subset of patients (reference range, 26.9 $\pm$ 2.5 pg/mL; Incstar Corp, Stillwater, MN). Normalized protein catabolic rate (nPCR) was calculated from urea generation rate and urea distribution volume by urea kinetic modeling.[14] Urea reduction ratio (URR) and nPCR were averaged for 3 months at enrollment. Note that because this was a dynamic cohort (in which patients entered the cohort at different times), only a subset of patients was assayed for serum aluminum and $1,25\text{-}(OH)_2D$, which were available only after January 1992.

Statistics

Statistical packages SPSS (version 10.0; SPSS Inc, Chicago, IL) and R (Available at: http://www.ci.tuwien.ac.at/~hornik/R/R-FAQ.html) were used. Results are expressed as mean $\pm$ SEM. Two-tailed tests were used. *P* less than 0.05 is considered statistically significant.

Because PTH level was not normally distributed, it was logarithmically transformed before statistical tests. In enrollment data, unpaired Student's *t*-tests were used to compare means between two groups, considering Levene's test for equality of variances. One-way analysis of variance, followed by Bonferroni test, was used for comparison among three groups. Chi-square tests with continuity correction were used for categorical variables. Pearson's product-moment correlation was performed for the relationship between two continuous variables. Multiple regression (dependent variable, PTH) was used to adjust

Table 1. Demographic and Biochemical Features in 126 HD Patients With and Without Enrollment Hypoparathyroidism

Variables	PTH < 65 pg/mL	No. of Patients	PTH = 65-200 pg/mL	No. of Patients	PTH > 200 pg/mL	No. of Patients
PTH (pg/mL)	32.4 ± 2.9	32	132.1 ± 6.26*	44	430 ± 27.9*†	50
Age (y)	60.9 ± 2.4	32	51.7 ± 1.7*	44	50 ± 2.1*	50
Duration (mon)	16.5 ± 4.7	32	11.8 ± 4.5	44	18.2 ± 3.2	50
Men (%)	34.4	32	46.5	44	45.1	50
Vitamin D use (%)	6.3	32	13.8	44	8.2	50
rHuEPO dosage (U/mon)	8,985 ± 1,085	32	8,261 ± 862	44	9,970 ± 786	50
Diabetes (%)	50	32	42.8	44	18*‡	50
Hemoglobin (g/dL)	9.37 ± 0.58	32	8.56 ± 0.39	44	9.47 ± 0.37	50
Ionized calcium (mg/dL)	5.08 ± 0.08	32	4.7 ± 0.06§	44	4.45 ± 0.05*‡	50
Phosphate (mg/dL)	4.46 ± 0.34	32	5.28 ± 0.23	44	6.18 ± 0.28*	50
Magnesium (mEq/L)	2.5 ± 0.1	19	2.3 ± 0.08	28	2.48 ± 0.09	41
Albumin (g/dL)	3.72 ± 0.08	32	3.76 ± 0.08	44	4.08 ± 0.08*	50
BUN (mg/dL)	89.4 ± 6.7	32	84.7 ± 3.1	44	101 ± 3.7‡	50
nPCR (g/kg/d)	1.0 ± 0.04	32	1.11 ± 0.03	44	1.18 ± 0.04*	50
URR	0.69 ± 0.03	32	0.68 ± 0.02	44	0.72 ± 0.01	50
Creatinine (mg/dL)	9.23 ± 0.39	32	11.2 ± 0.46§	44	13.4 ± 0.48*†	50
Aluminum (μg/L)	59.4 ± 4.3	22	54.8 ± 6.8	28	61 ± 4.23	31
$1,25(OH)_2D$ (pg/mL)	8.3 ± 2.8	20	8.1 ± 2.8	21	7.68 ± 4.2	23

NOTE. Values expressed as mean ± SEM.
*$P < 0.01$ versus PTH level less than 65 pg/mL.
†$P < 0.01$ versus PTH level of 65 to 200 pg/mL.
‡$P < 0.05$ versus PTH level of 65 to 200 pg/mL.
§$P < 0.05$ versus PTH level less than 65 pg/mL.

for multiple variables (diabetes, use of vitamin D, age, duration of dialysis therapy, rHuEPO dosage, hemoglobin level, ionized calcium level, phosphate level, albumin level, BUN level, creatinine level, and URR). Categorical variables (diabetes and use of vitamin D) were coded as 0 (absent) or 1 (present). Collinearity of independent variables was assessed by the variance inflation factor. In general, a variance inflation factor greater than 10 indicates significant collinearity.

In the longitudinal study, ordinary least squares are not adequate because serial data tend to be autocorrelated, and data within clusters (individuals) also are correlated.[15] Therefore, a generalized estimating equation[15] (dependent variable, PTH; independent variables, diabetes, use of vitamin D, age, duration of dialysis therapy, rHuEPO dosage, hemoglobin level, ionized calcium level, phosphate level, magnesium level, albumin level, creatinine level, aluminum level) was used to study factors affecting PTH. Survival analysis was performed using the Kaplan-Meier method (with log-rank test). Moreover, Cox proportional hazards regression (predictors: diabetes, age, duration of dialysis therapy, rHuEPO dosage, PTH levels at entry or serial PTH levels, hemoglobin level, albumin level, creatinine level, URR) was used, in which serial PTH levels were treated as time-dependent covariates. Patients studied were either dead, prematurely censored before April 2000 (eg, transferred to other hospitals, on peritoneal dialysis therapy, underwent renal transplantation), or censored on April 2000 (ie, alive by April 2000).

RESULTS

Risk Factors for Relative Hypoparathyroidism

Cross-sectional study in enrollment. Prevalences of absolute (PTH < 65 pg/mL) and relative hypoparathyroidism (PTH, 65 to 200 pg/mL) were 32 of 126 (25.4%) and 44 of 126 patients (34.9%), respectively. Mean PTH levels were 135 ± 1.1 pg/mL in patients administered calcium carbonate (n = 88) as the phosphate binder and 168 ± 1.4 pg/mL (P = not significant [NS]) in patients administered aluminum hydroxide (n = 12). As listed in Table 1, patients with a PTH level greater than 200 pg/mL were less likely to have diabetes and had lower ionized calcium and greater creatinine levels than those with a PTH level of 200 pg/mL or less. Patients with a PTH level greater than 200 pg/mL also had greater phosphate and albumin levels than those with a PTH level less than 65 pg/mL. Patients with a PTH level less than 65 pg/mL were older and had greater ionized calcium levels than those with a PTH level of 65 pg/mL or greater. Patients with a PTH level less than 65 pg/mL had lower nPCRs than those with a PTH

Table 2. Demographic and Biochemical Features in 126 HD Patients With and Without Diabetes

Variables	No Diabetes	No. of Patients	Diabetes	No. of Patients	*P*
PTH (pg/mL)	176 ± 1.13	86	76.7 ± 1.17	40	<0.001
Age (y)	50.4 ± 1.5	86	59.8 ± 1.6	40	<0.001
Duration (mon)	19.2 ± 2.6	86	9.3 ± 2.2	40	<0.01
Men/total	38/86 (44)	86	17/40 (43)	40	NS
Use of vitamin D	10/86 (12)	86	1/40 (2.5)	40	NS
Ionized calcium (mg/dL)	4.64 ± 0.04	86	4.8 ± 0.08	40	NS
Phosphate (mg/dL)	5.76 ± 0.19	86	4.71 ± 0.34	40	<0.01
Magnesium (mEq/L)	2.48 ± 0.28	63	2.38 ± 0.08	25	NS
Albumin (g/dL)	4.01 ± 0.05	86	3.54 ± 0.08	40	<0.001
BUN (mg/dL)	98 ± 2.7	86	80 ± 5	40	<0.01
URR	0.73 ± 0.01	86	0.63 ± 0.02	40	<0.001
Creatinine (mg/dL)	12.7 ± 0.34	86	9.2 ± 0.43	40	<0.001
Aluminum (μg/L)	61.3 ± 4.6	58	59.7 ± 8.4	23	NS
1,25$(OH)_2$D (pg/mL)	8.5 ± 0.45	43	8 ± 0.71	21	NS

NOTE. Results expressed as mean ± SEM or number of total (percent).

level greater than 200 pg/mL. Patients with a PTH level of 65 to 200 pg/mL had lower BUN levels than those with a PTH level greater than 200 pg/mL. However, there were no differences in duration of dialysis therapy, distribution of sex or vitamin D use, URR, or serum magnesium, aluminum, and 1,25$(OH)_2$D levels among these three groups of patients. Note that results are similar when the arbitrary cutoff value for PTH was changed from 200 to 162.5 pg/mL (2.5 times the normal upper limit).

As listed in Table 2, patients with diabetes had lower PTH levels and were older and had a shorter duration of dialysis therapy than patients without diabetes. Moreover, patients with diabetes had lower albumin, BUN, creatinine, and phosphate levels and URRs than those without diabetes. Conversely, no difference was found in sex, use of vitamin D, or levels of ionized calcium, magnesium, aluminum, or 1,25$(OH)_2$D between these two groups.

PTH level correlated with age ($r = -0.41$; $P < 0.001$), BUN level ($r = 0.26$; $P < 0.01$), creatinine level ($r = 0.56$; $P < 0.001$), URR ($r = 0.22$; $P < 0.05$), albumin level ($r = 0.40$; $P < 0.001$), ionized calcium level ($r = -0.58$; $P < 0.001$), and phosphate level ($r = 0.42$; $P < 0.001$) by univariate correlation analyses. Conversely, multiple regression analysis (Table 3) showed that PTH level correlated only with age ($P < 0.01$), ionized calcium level ($P < 0.001$), and creatinine level ($P < 0.001$). In the subset of data with no missing magnesium (n = 88) or aluminum values (n = 81), PTH level was not associated with magnesium or aluminum level. Collinearity diagnostics of independent variables showed that all variance inflation factors (range, 1.0 to 1.52) were much less than 10. In other words, there was no significant multicollinearity among independent variables.

Longitudinal study. PTH levels fluctuated in all patients, whereas 39 of 76 relatively hypoparathyroid (PTH ≤ 200 pg/mL) patients (51%) remained persistently hypoparathyroid. As listed in Table 4, a generalized estimating equation showed that time-dependent PTH levels were associated inversely with age and ionized calcium levels and directly with albumin and phosphate levels, duration of dialysis therapy, and use of vitamin D. The association between PTH and

Table 3. Stepwise Multiple Regression for Factors Associated with logPTH in 126 HD Patients in Enrollment

Variable	Coefficient ± SE	*P*	No. of Patients
Age (y)	−0.016 ± 0.006	<0.01	126
Ionized calcium (mg/dL)	−0.96 ± 0.16	<0.001	126
Creatinine (mg/dL)	0.11 ± 0.03	<0.001	126

NOTE. Dependent variable is logPTH; independent variables are diabetes, use of vitamin D, age, duration of dialysis therapy, rHuEPO dosage, hemoglobin level, albumin level, BUN level, creatinine level, PCR, URR, and ionized calcium and phosphate levels. Only results with *P* less than 0.05 are listed.

Table 4. Results of a Generalized Estimating Equation in the Longitudinal Study

Variable	Coefficient ± SE	*P*	No. of Data
Vitamin D use	0.4 ± 0.195	<0.05	1,971
Age (y)	−0.018 ± 0.0048	<0.02	1,971
Duration (y)	0.059 ± 0.025	<0.02	1,971
Ionized calcium (mg/dL)	−0.97 ± 0.1	<0.001	1,971
Phosphate (mg/dL)	0.11 ± 0.017	<0.01	1,971
Albumin (g/dL)	0.23 ± 0.07	<0.02	1,971
Magnesium (mEq/L)	−0.19 ± 0.09	<0.05	915

NOTE. Dependent variable is logPTH level (1,971 data points); independent variables are diabetes, vitamin D use, age, duration of dialysis therapy, rHuEPO dosage, and hemoglobin, albumin, creatinine, ionized calcium, and phosphate levels. Note that magnesium level was included in only a subset of patients with no missing magnesium values (915 data points). Only results with *P* less than 0.05 are listed.

ionized calcium/phosphate levels over time is shown in a representative patient (Fig 1). In subsets of data with no missing magnesium or aluminum values, time-dependent PTH levels also were associated inversely with magnesium levels (n = 915), but not aluminum levels (n = 601).

Glycemic Control and Hypoparathyroidism in Patients With Diabetes

In cross-sectional enrollment data, PTH level was not associated with either HbA_{1c} or glucose level in stepwise multiple regression. In the longitudinal study, time-dependent PTH levels also were not associated with glucose levels in data with no missing glucose (n = 1,067) or HbA_{1c} values (n = 261) in a generalized estimating equation.

Impact of PTH Levels at Entry and Time-Dependent PTH Levels on Mortality

During the 10-year follow-up of 126 patients, 46 patients (36.5%) died. Fifty-three of 126 patients (42.1%) were alive by April 2000, whereas 27 of 126 patients (21.4%) were censored before April 2000. Thirty-nine of 46 patients (84.8%) with enrollment hypoparathyroidism were among patients who died. Cause of death was cardiovascular in 19 of 46 patients (41.3%).

For a meaningful analysis of the following data, we must have enough patients while excluding those prematurely censored (eg, transferred to other hospitals, on peritoneal dialysis therapy, underwent renal transplantation) for whom data were not available. Therefore, the following analyses are performed in the 101 patients who were not censored, ie, either alive (n = 56) or dead (n = 45), by year 5 of follow-up. In patients with and without enrollment hypoparathyroidism, 17 of 63 (27%) and 2 of 38 patients (5.3%) had cardiovascular deaths ($P < 0.02$) and 5 of 63 (7.94%) and 2 of 38 patients (5.3%) had fractures (P = NS), respectively. Three of 45 (6.7%) and 4 of 56 patients (7.1%) had fractures among those who died or survived, respectively (P = NS). Patients who died had significantly lower values for albumin (3.6 ± 0.07 versus 3.95 ± 0.06 g/dL; $P < 0.01$) and nPCR (1.0 ± 0.03 versus 1.14 ± 0.04 g/kg/d; $P < 0.02$) than those who survived. As shown in Fig 2A, PTH levels increased with time only in patients who survived. Furthermore, as shown in Fig 2B, in patients with enrollment hypoparathyroidism (n = 63), persistence of hypoparathyroidism during the study only occurred in patients who died (n = 30).

Kaplan-Meier analysis showed that enrollment hypoparathyroidism (Fig 3A) was associated with mortality. Cox regression showed that enrollment hypoparathyroidism, but not nPCR, was independently associated with mortality af-

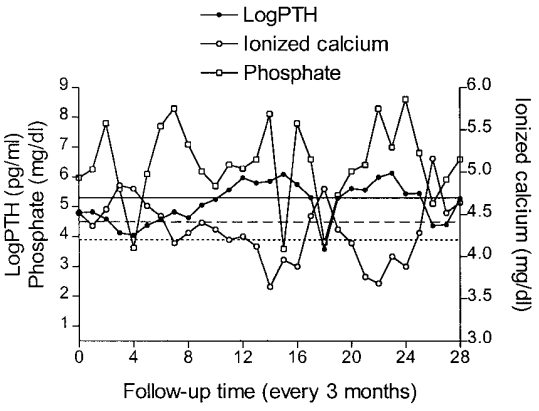

Fig 1. Serial PTH, ionized calcium, and phosphate levels in a representative patient. Note that PTH levels changed in the same and opposite directions of phosphate and ionized calcium levels. Horizontal lines are cutoff values for PTH (200 pg/mL; solid line), ionized calcium (4.2 mg/dL; lower broken line), and phosphate (4.5 mg/dL; upper broken line).

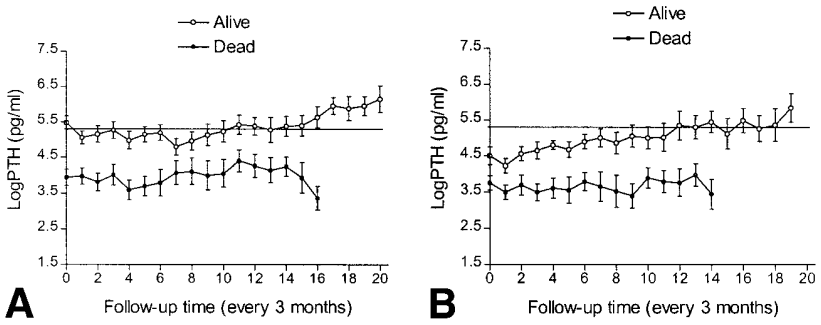

Fig 2. (A) Serial PTH levels in 101 patients who were not censored, ie, alive (n = 56) or dead (n = 45) by year 5 of follow-up. (B) Serial PTH levels in 63 patients with initial hypoparathyroidism who were either alive (n = 33) or dead (n = 30) by year 5 of follow-up. Horizontal line is the cutoff value for PTH (200 pg/mL).

ter adjusting for five traditional risk factors (diabetes, age, albumin level, creatinine level, and URR) and duration of dialysis therapy (Fig 3B).

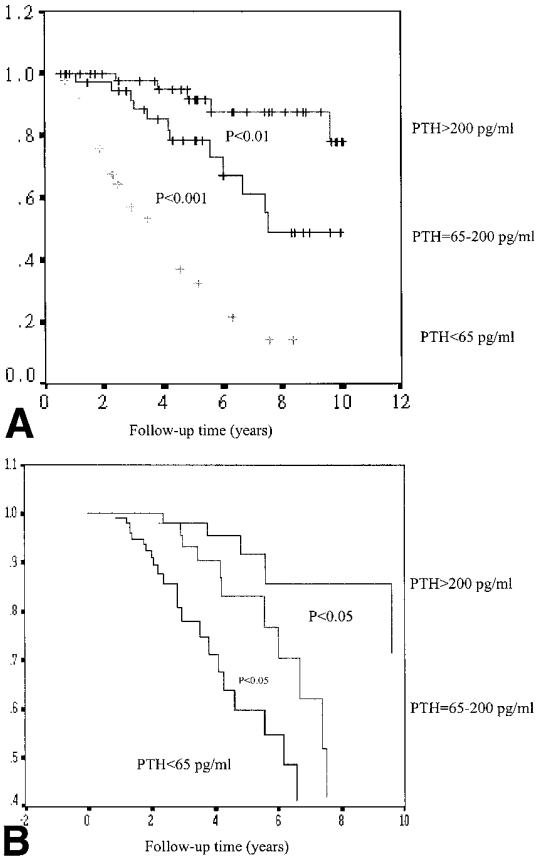

Fig 3. Cumulative survival by (A) Kaplan-Meier and (B) Cox proportional hazards survival analysis in 126 HD patients. Mortality was highest in patients with initial PTH levels less than 65 pg/mL and lowest in patients with initial PTH levels greater than 200 pg/mL either (A) before or (B) after adjustment for traditional risk factors (diabetes, age, albumin and creatinine levels, and URR) and duration of dialysis therapy.

In addition, time-dependent PTH levels (hazard ratio, 0.63 [range, 0.48 $\sim$ 0.84]; $P < 0.005$) also were independently associated with less mortality.

DISCUSSION

In the cross-sectional study, relatively hypoparathyroid patients were older, more likely to have diabetes, and had greater ionized calcium and lower phosphate, albumin, BUN, and creatinine levels. However, there was no difference in aluminum or $1,25(OH)_2D$ levels or URRs between patients with and without relative hypoparathyroidism. There also was no difference in PTH levels between patients administered either calcium carbonate or aluminum hydroxide alone as phosphate binders. Multiple regression showed that PTH level was only associated directly with creatinine level and inversely with age and ionized calcium level. In addition, mean enrollment serum aluminum level was high (53.5 to 62.1 μg/L) in patients. However, serum aluminum levels decreased with time (56.7 $\pm$ 7 and 24.3 $\pm$ 9.5 μg/L in 1992 and 2000, respectively) because of the increasing awareness of aluminum toxicity.

This was the first use of a longitudinal study to examine factors associated with time-dependent PTH levels within clusters (individual patients and subgroups of patients) and between clusters over time in HD patients. Thus, we found that uremic hypoparathyroidism was a time-dependent phenomenon modifiable by multiple factors. In addition, by increasing the number of observations (from 126 to 1,971 observations) and statistical power, five more risk factors (vitamin D use, duration of dialysis therapy, and albumin, phosphate, and magnesium levels) were

found in the longitudinal study than in the cross-sectional study.

The association between PTH and ionized calcium, phosphate, and magnesium levels in previous cross-sectional studies[4,5,16] was confirmed by our longitudinal study. This is important because we are concerned with relationships between PTH levels and these variables in individual patients over time instead of a population in cross-section. We also found that time-dependent PTH levels were associated directly with time-dependent serum albumin levels. Interestingly, albumin, BUN, creatinine, and phosphate are markers of nutrition.[17-19] Because relatively hypoparathyroid patients were older and had lower albumin, BUN, creatinine, and phosphate levels, whereas absolutely hypoparathyroid patients had lower nPCRs, we speculate that they were malnourished. PTH level was inversely associated with modified subjective global assessment in a recent cohort of our HD patients ($n = 79$; $P < 0.05$), in which a high score indicates malnutrition.[20] Similar speculation has been raised by a recent review on adynamic bone diseases with low PTH levels.[21] Two recent studies also showed that a low-protein diet induced uremic hypoparathyroidism.[22,23]

Note that attending physicians prescribed vitamin D in hyperparathyroid patients and withheld vitamin D in hypoparathyroid patients during the longitudinal study; therefore, vitamin D use was associated directly with PTH level. A recent study also failed to increase PTH levels in uremic hypoparathyroid patients despite withholding vitamin D for 11 months.[24] Of course, vitamin D treatment would predispose dialysis patients to hypoparathyroidism and adynamic bone disease in prospective studies.[25]

Diabetes has been associated with uremic hypoparathyroidism.[1,6,26] A 1990 study found that a high glucose level inhibits PTH secretion in cultured parathyroid cells.[27] A cross-sectional study also found an inverse association between plasma glucose and PTH levels in predialytic patients with diabetes by univariate analyses.[28] However, by using multivariate analyses, our cross-sectional and longitudinal studies did not show a relationship between diabetes per se and PTH level or glycemic control (short or long term) and PTH level. Therefore, we suggest that aging, short duration of dialysis therapy, hypophosphatemia, and hypoalbuminemia accounted for uremic hypoparathyroidism in patients with diabetes.

Secondary hyperparathyroidism is associated with rHuEPO resistance, whereas rHuEPO increases survival in prospective studies.[29] However, we found no association between PTH level, survival, and rHuEPO use and/or hemoglobin level in cross-sectional and longitudinal studies. We also have shown that rHuEPO failed to affect PTH level in a previous prospective study.[11] The lack of association between survival and rHuEPO use and/or hemoglobin level can be explained because this was a retrospective study, whereas Health Insurance Agencies require that the maximum hemoglobin level and rHuEPO dosage be kept at 10 g/dL and 20,000 U/mon, respectively.

The mechanism of uremic hypoparathyroidism is not known, although vitamin D receptor gene polymorphism has been proposed.[30] In addition, as in secondary hyperparathyroidism, a calcium-sensing receptor abnormality also is an intriguing possibility.[31] Decreased PTH responsiveness to hypocalcemia was even suggested by a study using the less specific C-terminal PTH assay in HD patients.[32] However, we did not find a difference in the slope of the PTH-ionized calcium regression curve between patients with and without hypoparathyroidism in the cross-sectional study. A similar finding was shown by a study of adynamic bone diseases.[33]

After adjusting for traditional risk factors (diabetes, age, albumin level, creatinine level, and URR)[16] and duration of dialysis therapy,[34] we found that hypoparathyroidism was independently associated with mortality in HD patients. Moreover, lower time-dependent PTH levels were independently associated with mortality. This observation is surprising because secondary hyperparathyroidism has been associated with many adverse effects in uremic patients.[3]

Because patients with adynamic bone disease can develop hypercalcemia,[35] one explanation is that uremic hypoparathyroidism is associated with vascular calcifications and cardiovascular complications.[36,37] Vascular calcification may cause arterial stiffening,[35,38] atherosclerosis, and mortality[38-40] in HD patients. Administration of calcium and vitamin D often leads to hypercalcemia, relative hypoparathyroidism, and tissue cal-

cification.[37,38,41] We found that cardiovascular mortality was more prevalent in patients with enrollment hypoparathyroidism.

A second explanation is that uremic hypoparathyroidism may be associated indirectly with mortality by its association with malnutrition. Thus, we found that patients who died had lower albumin levels and nPCRs than those who survived by year 5. However, multivariate survival analysis showed that survival was associated with albumin level, but not nPCR. This observation was corroborated by another large study.[42] Dissociation of albumin level and nPCR in survival analysis may be explained because hypoalbuminemia is the combined result of malnutrition and inflammation, whereas inflammation per se also can increase mortality in HD patients.[18]

A third explanation is that uremic hypoparathyroidism is associated with increased fractures, which have high mortality rates.[43,44] However, we found that fracture was not more prevalent in patients who died or those with enrollment hypoparathyroidism by year 5 of follow-up. Finally, the possibility that severe hyperparathyroidism may be associated with mortality cannot be ruled out in this study because we excluded patients with a previous parathyroidectomy and intravenous high-dose active vitamin D treatment.

It is tempting to speculate that treating uremic hypoparathyroidism may decrease mortality. Unfortunately, there is no known treatment for uremic hypoparathyroidism.[2] However, we found that PTH levels fluctuated and the state of relative hypoparathyroidism was changeable in 49% of hypoparathyroid patients. In addition, among risk factors found in the longitudinal study, calcium, phosphate, and magnesium levels can be modulated. Unfortunately, traditional therapies for renal osteodystrophy have potentially adverse clinical consequences.[35-38,41,45] For example, it is almost impossible to control hyperphosphatemia with diet without inducing malnutrition.[46] Accordingly, novel therapies (calcium and aluminum-free phosphate binders, vitamin D analogues with minimal calcemic effects, and calcimimetic agents) have been designed to reduce the risk for calcification.[45] It remains to be seen whether these therapies will prevent relative hypoparathyroidism in HD patients.

We used dialysate calcium concentrations of 2.5 to 3.5 mEq/L. Current recommendations for dialysate calcium are approximately 2.5 to 3.5 mEq/L for patients administered calcium, 3.3 to 3.5 mEq/L for patients not administered calcium, and 2.5 to 3.0 mEq/L for patients on vigorous vitamin D therapy or with hypercalcemia.[47] A low calcium dialysate level (2.5 mEq/L)[48,49] and phosphate supplement can reverse uremic hypoparathyroidism.[4] Avoidance of vitamin D overuse also is a prudent choice. Finally, it remains to be seen whether improving nutrition ameliorates uremic hypoparathyroidism.

We conclude that relative hypoparathyroidism was prevalent in HD patients, although not associated with diabetes per se. Time-dependent PTH levels fluctuated with time and were associated with age, duration of dialysis therapy, and time-dependent ionized calcium, phosphate, albumin, and magnesium levels. Moreover, relative hypoparathyroidism at entry and lower time-dependent PTH levels predict mortality.

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