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Original Article

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Serum Parathyroid Hormone Levels and All-Cause Mortality Risk in Hemodialysis Patients in the Black Sea Region of Türkiye

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ABSTRACT

Objective: The association between serum parathyroid hormone levels and the all-cause mortality risk in patients with chronic kidney disease grade 5 treated by hemodialysis was examined.
Methods: A total of 408 hemodialysis patients living in the Black Sea region of Türkiye were included in this study. Cox proportional hazards regression analysis was performed.
Results: The median age of patients was 64 (57-71) years. The median follow-up duration was 51 (28-60) months. During follow-up, 205 (50.2%) patients died. In the multivariable-adjusted analysis, the time-averaged serum parathyroid hormone level of 450-599 pg/mL had the lowest mortality risk. The all-cause mortality risk was elevated in patients with time-averaged parathyroid hormone— levels of <150 and ≥600 pg/mL. Patients with a time-averaged corrected serum calcium level of ≥9.5 mg/dL and a time-averaged serum phosphorus level of <4.0 mg/dL also had increased all-cause mortality risk.
Conclusion: The all-cause mortality risk was increased in hemodialysis patients with time-averaged parathyroid hormone levels of <150 and ≥600 pg/mL. Hypercalcemia and hypophosphatemia also increased the all-cause mortality risk.
Keywords: All-cause mortality, calcium, hemodialysis, parathyroid hormone

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INTRODUCTION

Chronic kidney disease–mineral and bone disorder (CKD-MBD) is an important problem in CKD grade 5 treated by dialysis patients. Abnormal changes in bone and vascular or soft tissue calcification can also be seen with biochemical changes.[1] Extraosseous calcification can cause arterial, valvular, and myocardial calcification. Cardiovascular calcification causes increased cardiovascular events and death in CKD grade 5 treated by dialysis patients.[1,2] Chronic kidney disease–mineral and bone disorder can lead to fracture development which increases the death rate in dialysis patients.[3] Chronic kidney disease–mineral and bone disorder is a significant reason for morbidity and mortality.[1]

There is a linkage between serum calcium, phosphorus, parathyroid hormone (PTH) levels, and all-cause mortality. Parathyroid hormone levels connected with the lowest and highest all-cause mortality risk were investigated in different studies.[4-10] However, different results were obtained for PTH levels connected with the all-cause mortality risk.[4-10] In general, there is a U-shaped linkage between serum PTH levels and the mortality risk.[6-10] The Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD guideline recommends that the target intact PTH level be sustained between 2 and 9 times the upper normal limit.[1] The Japanese CKD-MBD guideline recommends keeping PTH between 60 and 240 pg/mL.[11]

We examined the connection between serum time-averaged PTH levels and all-cause mortality risk in CKD grade 5 treated by hemodialysis patients in the Black Sea region of Türkiye. We also investigated the

relationship between serum time-averaged corrected calcium, time-averaged phosphorus levels related to CKD-MBD and all-cause mortality risk.

METHODS

Patients

This study was carried out with 408 incident and prevalent hemodialysis patients in 4 outpatient hemodialysis clinics in the Black Sea region of Türkiye. All patients were diagnosed with CKD grade 5 which was treated by hemodialysis. Patients with acute kidney injury treated by hemodialysis were not included in this study. Patients who were admitted to these hemodialysis centers between January 2011 and January 2016 were included in the study. The 5-year follow-up period of the patients was evaluated retrospectively. Patients with less than 6 months of follow-up were excluded from the study. Patients with missing data and those with parathyroidectomy were eliminated from the study. Data of patients who died during this period; went to other hemodialysis clinics, underwent kidney transplantation, and switched to peritoneal dialysis were assessed during their follow-up duration. We did not have any patients with coronavirus disease 2019 infection in the follow-up duration. This study has the local Ethics Committee permission (2021/525). Informed consent could not be obtained from all patients because our study was a retrospective data review. The study was conducted retrospectively, so informed consent was not provided for all patients.

Patients' ages and the hemodialysis vintage were recorded. Diabetes Mellitus (DM) status of the patients was recorded. The vascular access type that the patients had at the end of the follow-up was also recorded. The patients were separated into 2 groups in terms of the vascular access type: those with an arteriovenous fistula/arteriovenous graft and those with a central venous catheter.

We used levels of 150 and 600 pg/mL as lower and upper limits, respectively. The patients were separated into 5 groups in terms of time-averaged PTH results [PTH (pg/mL) <150, 150-299, 300-449, 450-599, and ≥600].

MAIN POINTS

- Chronic kidney disease–mineral and bone disorder (CKD-MBD) is an important problem in CKD grade 5 treated by hemodialysis patients.
- In the multivariable-adjusted analysis, time-averaged parathyroid hormone levels of <150 and ≥600 pg/mL demonstrated elevated all-cause mortality risk.
- The time-averaged corrected calcium level of ≥9.5 mg/dL was significantly related to elevated all-cause mortality risk.

Time-averaged serum phosphorus levels were divided into 3 groups: <4.0, 4-5.49, and ≥5.5 mg/dL.[7,8] Time-averaged serum corrected calcium levels were divided into 3 categories: <8.4, 8.5-9.49, and ≥9.5 mg/dL.

The effects of age, gender, hemodialysis vintage, DM, albumin, hemoglobin, single pool urea Kt/V (spKt/V), C-reactive protein (CRP), ferritin, and vascular access type were included in multivariable analysis.

Patients current therapies were managed by the participating clinics according to the KDIGO guidelines. [1,12-14]

Biochemical Tests

The laboratory test results of the patients were obtained retrospectively from their records. In hemodialysis centers, the serum phosphorus, corrected calcium, albumin, and hemoglobin levels were measured every month. The serum ferritin, transferrin saturation, PTH, uric acid, and CRP levels were measured every 3 months. The spKt/V was calculated every month.[15] Laboratory data performed at monthly and 3-month intervals were evaluated retrospectively. The average of all laboratory levels was assessed during the patients' follow-up duration. The time-averaged data of all laboratory data were used. Corrected calcium was computed in patients with serum albumin levels of <4.0 g/dL. Corrected calcium was calculated with the formula: "Corrected calcium, mg/dL = [0.8 × (4 − serum albumin, g/dL)] + measured calcium, mg/dL."

Statistical Analysis

Statistical Package for the Social Sciences model 21.0 (IBM Corp., Armonk, NY, USA) was benefited during data analysis. The conformity of variables to normal distribution was examined with the Kolmogorov–Smirnov test. Descriptive analyses were given with the means and SDs for normally distributed variables. The median and interquartile range were used for non-normal distributed variables. One-way analysis of variance test was used for parameters with normal distribution to compare groups, according to the PTH level. Groups were compared with the Kruskal–Wallis test for parameters not demonstrating normal distribution. The chi-square test was used to compare groups regarding frequency differences.

The Cox proportional hazards regression analysis was used in the multivariable-adjusted model to evaluate independent risk factors linked to all-cause mortality. In the multivariable-adjusted model, age, gender, hemodialysis vintage, DM status, time-averaged corrected calcium, time-averaged phosphorus, time-averaged PTH, time-averaged albumin, time-averaged hemoglobin, time-averaged spKt/V, time-averaged CRP, time-averaged ferritin, and vascular access types were included in the Cox regression analysis. Cases in which the *P*-value was <.05 were accepted to be statistically significant.

RESULTS

This study was conducted with 408 CKD grade 5 hemodialysis patients, of which 194 (47.5%) were female and 214 (52.5%) were male. The median age of patients was 64 (57-71) years. The median follow-up period of the patients was 51 (28-60) months. Two hundred five (50.2%) patients died during follow-up. Twenty-one (5.1%) patients underwent kidney transplantation. Twelve (2.9%) patients went to another hemodialysis center. Three (0.7%) patients were switched to peritoneal dialysis. One-hundred forty (34.3%) patients had DM.

The patients were separated into 5 groups in terms of time-averaged PTH results (Table 1). There was a statistically significant difference between PTH groups for age, hemodialysis vintage, DM frequency, serum phosphorus, corrected calcium, PTH, albumin, hemoglobin, CRP, and mortality rate (Table 1).

The all-cause mortality risk was assessed according to time-averaged PTH levels in the multivariable-adjusted model. The lowest mortality rate among PTH groups was between 450 and 599 pg/mL, so this range was used as a reference. In the multivariable adjusted analysis, time-averaged PTH levels <150 and ≥600 pg/mL showed higher all-cause mortality risk (Table 2). Multivariable Cox regression survival plot according to PTH groups is presented in Figure 1.

When time-averaged phosphorus levels were <4 mg/dL in the multivariable adjusted analysis, all-cause mortality risk was high (Table 2). In the multivariable adjusted analysis, there was a significantly increased all-cause mortality risk in the group with time-averaged corrected calcium levels of ≥9.5 mg/dL (Table 2). Other risk factors linked with all-cause mortality in hemodialysis patients are also demonstrated in Table 2. Other risk factors affecting mortality were advanced age, male gender, use of catheter as arteriovenous route, low time-averaged albumin levels, low time-averaged spKt/V values, and high time-averaged ferritin levels (Table 2).

DISCUSSION

We showed that the all-cause mortality risk is increased in hemodialysis patients with serum time-averaged PTH levels of <150 and ≥600 pg/mL in the multivariable adjusted analysis. Patients with serum time-averaged phosphorus levels of <4 mg/dL and time-averaged corrected calcium levels of ≥9.5 mg/dL had increased all-cause mortality risk.

The connection between serum PTH levels and mortality risk in CKD grade 5 treated by dialysis patients was shown in various studies. However, different results were obtained for the PTH levels associated with mortality.[4-10] The use of baseline, time-dependent, or time-averaged PTH data may have caused different results. In a study conducted with dialysis patients in Europe, increased all-cause mortality risk was found when time-dependent PTH levels were <150 and >300 pg/mL.[7] Tentori et al[5] found increased mortality risk when PTH levels were >600 pg/mL in the time-dependent and baseline models in their study of

Table 1. Comparison of Patient Parameters According to Time-Averaged Parathyroid Hormone Levels

Variables	PTH <150 pg/mL (n = 42)	PTH 150-299 pg/mL (n = 124)	PTH 300-449 pg/mL (n = 137)	PTH 450-599 pg/mL (n = 54)	PTH ≥600 pg/mL (n = 51)	*P*
Gender, female, n (%)	22 (52.4)	50 (40.3)	68 (49.6)	28 (51.9)	26 (51)	.424
Age (years)	67 (62-75)	66 (60-74)	64 (57-72)	61 (50-67)	59 (50-69)	<.0001
Hemodialysis vintage (months)	43 (18-60)	60 (33-73)	60 (51-111)	79 (60-153)	130 (92-205)	<.0001
DM, n (%)	20 (47.6)	50 (40.3)	48 (35)	14 (25.9)	8 (15.7)	.005
Phosphorus, mg/dL	4.38 ± 0.62	4.59 ± 0.73	4.82 ± 0.76	5.32 ± 0.69	5.37 ± 0.56	<.0001
Corrected calcium, mg/dL	8.93 (8.64-9.22)	8.75 (8.46-9.04)	8.85 (8.63-9.14)	9.0 (8.75-9.35)	9.21 (8.86-9.62)	<.0001
PTH, pg/mL	108 (79-126)	227 (181-262)	363 (329-404)	501 (478-540)	765 (648-994)	<.0001
Albumin, g/dL	3.80 (3.43-3.96)	3.91 (3.68-4.07)	3.98 (3.78-4.14)	3.94 (3.77-4.17)	3.97 (3.77-4.16)	<.0001
Hemoglobin, g/dL	11.06 (10.12-11.50)	11.15 (10.31-11.86)	11.26 (10.75-12.07)	11.23 (10.67-11.92)	11.60 (10.87-11.96)	.026
C-reactive protein, mg/L	18.42 (10.31-29.06)	16.66 (8.10-27.04)	11.38 (7.19-19.11)	10.83 (6.39-22.02)	12.94 (7.79-23.65)	.005
Uric acid, mg/dL	5.66 ± 0.95	5.91 ± 0.85	5.90 ± 0.88	5.82 ± 0.72	6.01 ± 0.78	.326
spKt/V urea	1.62 ± 0.29	1.66 ± 0.29	1.66 ± 0.27	1.64 ± 0.26	1.68 ± 0.24	.855
TSAT, %	26.27 (23.40-34.21)	28.46 (23.44-33.26)	27.76 (22.23-31.63)	28.89 (23.19-34.69)	27.06 (22.44-31.50)	.498
Ferritin, ng/mL	539 (373-974)	577 (400-786)	532 (398-784)	554 (443-808)	537 (387-927)	.915
Death, n (%)	35 (83.3)	67 (54.0)	61 (44.5)	19 (35.2)	23 (45.1)	<.0001
Vascular access, catheter, n (%)	17 (40.5)	32 (25.8)	34 (24.8)	12 (22.2)	12 (23.5)	.267

Data are presented as mean ± SD, median (interquartile range 25%-75%), and n (%).
Parathyroid hormone, corrected calcium, phosphorus, albumin, hemoglobin, spKt/V, C-reactive protein, uric acid, TSAT, and ferritin values are given as time-averaged.
DM, diabetes mellitus; PTH, parathyroid hormone; TSAT, transferrin saturation.

Table 2. Multivariable Adjusted Cox Regression Analysis for All-Cause Mortality

Variables	Number of Patients, n (%)	HR	95% CI	*P*
Gender				
Female	194 (47.5)	Reference		
Male	214 (52.5)	1.509	1.061-2.146	.022
Age	408 (100)	1.035	1.019-1.051	<.0001
Diabetes mellitus	140 (34.3)	1.300	0.972-1.740	.077
Vascular access				
Fistula/graft	301 (73.8)	Reference		
Catheter	107 (26.2)	2.276	1.659-3.122	<.0001
Parathyroid hormone, pg/mL				
<150	42 (10.3)	2.006	1.062-3.784	.032
150-299	124 (30.4)	1.405	0.796-2.480	.240
300-449	137 (33.6)	1.210	0.706-2.074	.489
450-599	54 (13.2)	Reference		
≥600	51 (12.5)	1.950	1.034-3.678	.039
Corrected calcium, mg/dL				
<8.4	54 (13.2)	1.144	0.733-1.785	.553
8.4-9.49	311 (76.2)	Reference		
≥9.5	43 (10.5)	2.007	1.261-3.195	.003
Phosphorus, mg/dL				
<4.0	56 (13.7)	1.586	1.061-2.373	.025
4.0-5.49	265 (65)	Reference		
≥5.5	87 (21.3)	1.252	0.821-1.911	.297
Albumin, g/dL	408 (100)	0.309	0.188-0.506	<.0001
Hemoglobin, g/dL	408 (100)	0.890	0.761-1.040	.143
spKt/V urea	408 (100)	0.446	0.217-0.914	.027
C-reactive protein, mg/L	408 (100)	0.999	0.991-1.007	.821
Ferritin, ng/mL	408 (100)	1.001	1.000-1.001	<.0001

Variables were adjusted for age, gender, hemodialysis vintage, diabetes mellitus, parathyroid hormone, corrected calcium, phosphorus, albumin, hemoglobin, spKt/V, C-reactive protein, ferritin, and vascular access type.
Parathyroid hormone, corrected calcium, phosphorus, albumin, hemoglobin, spKt/V, C-reactive protein, and ferritin values are time-averaged.
HR, hazard ratio.

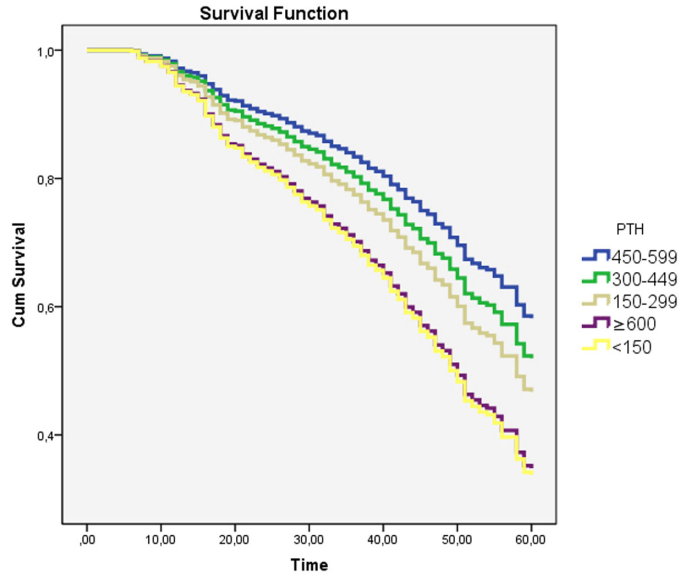

Figure 1. Multivariable Cox regression survival plot according to parathyroid hormone (PTH) groups.

hemodialysis patients. No elevated all-cause mortality risk was detected with low PTH levels. Block et al[4] found increased mortality risk when baseline PTH was ≥600 pg/mL, but no increase in mortality risk was found with low PTH levels. In a study conducted in China, baseline data were used and increased all-cause mortality risk was found in those with PTH levels of <150 and ≥450 pg/mL.[10] In a study conducted in Japan, high mortality risk was found when the PTH levels were >300 and ≤60 pg/mL at baseline, time-dependent, and time-averaged models.[8] In our study, all-cause mortality risk was higher in hemodialysis patients with time-averaged PTH levels of <150 and ≥600 pg/mL This is consistent with the KDIGO CKD-MBD guideline targets.[1] Unlike other studies, we used the time-averaged PTH data. Some studies, however, used baseline laboratory data.[4-10] Time-averaged PTH levels show the clinical situation for the long term more clearly. In follow-up, the serum calcium, phosphorus, and PTH levels can change over time. Patients with high phosphorus levels might have increased PTH levels during the follow-up.[16] Phosphorus binders, calcitriols, vitamin D analogs, and calcimimetics administered to patients affect the serum calcium, phosphorus, and PTH levels.[1,6] In patients with malnutrition-inflammation, serum phosphorus levels decrease during follow-up. Low phosphorus levels may cause a decrease in PTH levels.[6] Therefore, time-averaged PTH levels give more accurate results for mortality risk than baseline PTH.

Vascular calcification is one of the most significant reasons for mortality in dialysis patients with secondary hyperparathyroidism.[2] Hyperphosphatemia and hypercalcemia in secondary hyperparathyroidism are among the factors related to vascular calcification.[2,17] The patient group with PTH of ≥600 pg/mL had the highest corrected calcium and phosphorus levels (Table 1). In patients with PTH levels of <150 pg/mL, mortality might be due to malnutrition or vascular calcification. Dietary phosphorus intake is associated with protein intake. Low dietary protein intake creates low serum phosphorus and PTH levels in dialysis patients, which leads to malnutrition.[18] As such malnutrition correlates with mortality in dialysis patients.[19] The patient group with PTH levels of <150 pg/mL had the lowest serum albumin and phosphorus levels (Table 1). This can

indicate protein intake deficiency. Vascular calcification may also occur in patients with low PTH levels due to low bone turnover disease.[20]

Patients with serum time-averaged corrected calcium level of ≥9.5 mg/dL had increased all-cause mortality risk. There was no significant increased mortality risk in patients with hypocalcemia. In almost all studies seen in the literature, increased serum calcium levels were associated with mortality.[5-9] However, assessed serum calcium levels differ among studies. Some used the corrected calcium level, while others used the total calcium level. In addition, the relationship between baseline, time-dependent, or time-averaged serum calcium levels and all-cause mortality was investigated. Therefore, the serum calcium level associated with mortality differs between studies.[5-10] Floege et al[7] found increased mortality risk when the total serum calcium levels were >11.02 and <8.42 mg/dL in the time-dependent model. Tentori et al[5] found increased mortality risk when the corrected calcium level was >9.5 mg/dL in the time-dependent model, but there was no significantly increased risk in hypocalcemia. Kalantar-Zadeh et al[6] found increased mortality risk when the corrected calcium level was >10.5 mg/dL in the time-dependent model. In a study from Japan, increased mortality risk was found when the time-averaged corrected calcium levels were >9.5 and ≤8.5 mg/dL.[8] The relationship of hypercalcemia with mortality was generally attributed to vascular calcification due to increased calcium load.[21,22]

While the time-averaged serum phosphorus level was <4 mg/dL, there was an increased all-cause mortality risk. In our study, the mortality risk increased even when the phosphorus level was ≥5.5 mg/dL, although this increase was not statistically significant. The connection between serum phosphorus levels and mortality in dialysis patients is generally U-shaped. In a study conducted in Japan, increased mortality risk was found when time-averaged serum phosphorus levels were ≤4 and >5.5 mg/dL.[8] Tentori et al[5] found increased all-cause mortality risk when serum phosphorus levels were <3.5 and >7.0 mg/dL in a time-dependent model. Lertdumrongluk et al[23] investigated the time-averaged phosphorus level and risk of all-cause mortality in CKD grade 5 treated by hemodialysis patients. Hyperphosphatemia (>5.5 mg/dL) was related to increased risk of all-cause and cardiovascular mortality. A phosphorus level of <3.5 mg/dL was related to higher all-cause mortality risk only in those patients ≥65 years. Hypophosphatemia is generally linked to lower protein and calorie intake in hemodialysis patients.[24] Low daily protein intake and hypoalbuminemia led to increased mortality in dialysis patients.[13,25]

This study has some limitations. We did not find a statistically significant increased mortality risk when the serum phosphorus level was ≥5.5 mg/dL. This may result from a small number of patients with time-averaged phosphorus levels of ≥5.5 mg/dL, as most received daily phosphorus-binder therapy. When classifying patients according to phosphorus levels, we used the lower limit of 4 mg/dL, as the number of patients with time-averaged phosphorus of <3.5 mg/dL was low. Since most of the patients used calcimimetics for secondary hyperparathyroidism, patients with time-averaged corrected serum calcium levels of ≥10 mg/dL also appeared low. We used the upper limit as 9.5 mg/dL if classifying patients per corrected calcium levels.

In conclusion, hemodialysis patients have the highest all-cause mortality risk when serum time-averaged PTH levels were <150 and ≥600 pg/mL. Patients with time-averaged corrected calcium level of ≥9.5 mg/dL have increased all-cause mortality risk. Keeping the serum-corrected calcium level below this value for hemodialysis patients may reduce mortality. Hemodialysis patients with hypophosphatemia also have increased all-cause mortality risk.

Ethics Committee Approval: The study was approved by the Ethics Committee of Ondokuz Mayıs University (Approval Date: November 11, 2021; Approval Number: 2021/525).

Informed Consent: N/A.

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