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Association of Relatively Low Serum Parathyroid Hormone with Malnutrition-Inflammation Complex and Survival in Maintenance Hemodialysis Patients

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Abstract

Background—Low serum parathyroid hormone (PTH) has been implicated as a primary biochemical marker of adynamic bone disease in individuals with chronic kidney disease (CKD) who undergo maintenance hemodialysis (MHD) treatment. We hypothesized that the malnutrition-inflammation complex is associated with low PTH levels in these patients and confounds the PTH-survival association.

Methods—We examined 748 stable MHD outpatients in Southern California and followed them for up to 5 years (10/2001-12/2006).

Results—In 748 MHD patients, serum PTH <150 pg/ml was more prevalent among non-Blacks and diabetics. There was no association between serum PTH and coronary artery calcification score, bone mineral density or dietary protein or calorie intake. Low serum PTH was associated with markers of protein-energy wasting and inflammation, and this association confounded the relationship between serum PTH and alkaline phosphatase. Although 5-year crude mortality rates were similar across PTH increments, after adjustment for the case-mix and surrogates of malnutrition and inflammation, a moderately low serum PTH in 100 to 150 pg/ml range was associated with the greatest survival compared to other serum PTH levels, i.e., a death hazard ratio

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of 0.52 (95% confidence interval: 0.29-0.92, p<0.001) compared to PTH of 300 to 600 pg/ml (reference).

Conclusions—Low serum PTH may be another facet of the malnutrition-inflammation complex in CKD, and after controlling for this confounder, a moderately low PTH in 100 to 150 pg/ml range appears associated with the greatest survival. Limitations of observational studies should be considered.

Keywords

Parathyroid hormone (PTH); adynamic bone disease; malnutrition-inflammation complex; alkaline phosphatase; paricalcitol; cytokines

Introduction

Renal osteodystrophy, also known as “mineral-and-bone disorder” (MBD), is common in patients with chronic kidney disease (CKD) stage 5 who require maintenance dialysis treatment to survive.[1] The spectrum of disorders associated with CKD-MBD includes active vitamin D deficiency and secondary hyperparathyroidism, conditions that usually lead to *high-turnover* bone disease.[2-4] In recent years, however, heightened attention has also been devoted to the so-called “adynamic bone disease”, which is associated with attenuated osteoclastic and osteoblastic activity and other features of *low turnover* bone which may also include low serum parathyroid hormone (PTH).[5, 6] Adynamic bone disease is reported to develop more frequently among diabetic patients and those with advanced age, non-black race and undergoing peritoneal dialysis.[7, 8]

In addition to adynamic bone disease, there may be other factors associated with a low serum PTH concentration including hypercalcemia, high calcium load, and administration of vitamin D products or active vitamin D analogs and/or calcium sensing receptor antagonists (calcimimetics).[9-11] The *Kidney Disease Outcome Quality Initiative* (KDOQI) guidelines of the *National Kidney Foundation* recommended the target range of 150 to 300 pg/ml for serum PTH in CKD stage 5 and suggested withholding active vitamin D and/or calcimimetics if serum PTH is below 150 pg/ml.[12] These recommendations are set forth despite the fact that the normal range of the serum PTH in the general population is below 65 pg/ml.[13, 14] Indeed high-normal levels in 50 to 65 pg/ml range may be suggestive of hyperparathyroidism in the general population.[15]

It has recently been suggested that a low serum PTH may also happen in the setting of the malnutrition-inflammation-complex syndrome (MICS).[16] However, the association between low PTH and chronic inflammation [17] or protein-energy wasting [18] has not been well studied. Whereas the association between high serum PTH (>300 pg/ml) and increased mortality has been shown relatively consistently in most recent studies in CKD patients,[10, 19] there are mixed data about the association of low serum PTH (<150 pg/ml) and survival in this population.[19, 20] Parathyroidectomy usually leads to low PTH values and is associated with a long-term survival benefit and fewer fractures.[21] It is not known whether survival varies across different ranges of the so-called “low” serum PTH including low normal (150 to 200 pg/ml), borderline low (100 to 150 pg/ml) and the lowest levels (<100 pg/ml). Indeed, two recent studies showed that lowest PTH values were associated with the greatest survival in CKD patients.[10, 22] Moreover, withholding PTH suppressing medications in such low PTH ranges, e.g. in order to comply with the KDOQI or other guidelines, may have a bearing on survival, especially since active vitamin D analogs may be associated with greater survival [23] and decreased hospitalization.[24] Hence, we examined the hypotheses that low serum PTH is associated with malnutrition-inflammation

complex and that the relatively low ranges of PTH are associated with greater survival especially after controlling for the confounding by the MICS and less frequent administration of active vitamin D medications.

Methods

Patient Population

We studied maintenance hemodialysis (MHD) patients who participated in the Nutritional and Inflammatory Evaluation in Dialysis (NIED) Study (see the NIED Study website at www.NIEDStudy.org for more details, as well as previous publications).[25-31] Subjects were randomly selected from a pool of over 3,000 MHD outpatients in eight *DaVita* chronic dialysis facilities in the South Bay Los Angeles area.[32] Inclusion criteria were outpatients who had been undergoing MHD for at least eight weeks, who were 18 years or older and who signed the Institutional Review Board approved consent form. Patients with an anticipated life expectancy of less than 6 months (e.g. due to a metastatic malignancy or advanced HIV/AIDS disease) were excluded. From October 1, 2001, through December 31, 2006, 893 MHD patients signed the informed consent form and underwent the periodic evaluations of the NIED Study. For this study, data including serum PTH were available in 748 MHD patients. Furthermore, 167 of these individuals were randomly selected to undergo additional tests at the General Clinical Research Center (GCRC) at Harbor-UCLA as parts of the “NIED Substudy”.[32]

The medical chart of each MHD patient was thoroughly reviewed by a collaborating physician and data pertaining to the underlying kidney disease, cardiovascular history and other comorbid conditions were extracted. A modified version of the Charlson comorbidity index, i.e., without the age and kidney disease components, was used to assess the severity of comorbidities.[33, 34] The 748 MHD patients were followed for up to 63 months, i.e., until December 31, 2006.

Nutritional Evaluation, Bone Density and Coronary Calcification

Body weight assessment and anthropometric measurements were performed while patients underwent a hemodialysis treatment or within 5 to 20 minutes after termination of the treatment. Biceps skinfold (BSF) and triceps skinfold (TSF) thicknesses were measured with a conventional skinfold caliper using standard techniques as previously described.[35, 36] The Malnutrition-Inflammation Score (MIS) was assessed based on its 10 components at 4 levels of severity from 0 (normal) to 3 (severely abnormal) and included five nutritional history criteria (weight change, dietary intake, gastrointestinal symptoms, functional capacity, and comorbid conditions), two physical examination components (subcutaneous body fat and signs of muscle wasting) body mass index (>20, 18 to 19.99, 16 to 17.99, and <16 kg/m^2), and serum albumin (≥4.0, 3.5–3.9, 3.0–3.4 and <3.0 g/dL) and the total iron binding capacity (TIBC) concentrations (≥250, 200–249, 150–200, and <150 mg/dL). The sum of all 10 MIS components can range from 0 (normal) to 30 (severely malnourished).[37]

To estimate the percentage of body fat and fat-free body mass, near infra-red (NIR) interactance was measured at the same time as the anthropometric measurements[38] using commercial NIR sensor with a coefficient of variation of 0.5% for total body fat measurement (portable Futrex 6100®, Gaithersburg, Maryland, www.futrex.com). NIR measurements were performed by placing, for several seconds on the upper aspect of the arm without a vascular access, a Futrex® sensor, and entering the required data (date of birth, gender, weight and height) of each patient. NIR measurements of body fat appear to correlate significantly with other nutritional measures in MHD patients.[39]

In the subgroup of patients who attended the NIED Substudy for additional tests were performed: Dual energy X-ray absorptiometry (Hologic fan-beam QDR-4500-Delphi-A, Software: QDR for Windows XP version 12.4.Hologic Inc.35 Crosby Drive, Bedford, MA) was used to estimate bone density. Electron beam computed tomography (EBCT) using an Imatron C-150XL ultrafast computed tomography scanner (GE-Imatron, South San Francisco, California) was used to image coronary arteries at 3-millimeter intervals, and the number of calcified lesions was totaled for each coronary artery to obtain total coronary artery calcification score.[40] Three-day diet recall with a subsequent interview was performed to estimate the total daily protein and calorie intake.[41]

Laboratory Tests and Medications

Pre-dialysis blood samples and post-dialysis serum urea nitrogen were obtained on a mid-week day which coincided chronologically with the drawing of quarterly blood tests in the DaVita facilities. The single-pool Kt/V was used to represent the weekly dialysis dose. Serum intact PTH was measured via first generation immuno-radiometric PTH assay (Nichols, San Juan Capistrano, CA) [42] All routine laboratory measurements were performed by *DaVita*® Laboratories (Deland, FL) using automated methods. Patients who were administered active vitamin D received injectable paricalcitol (Abbott Laboratories, Abbott Park, IL). The 3-month averaged values of each routine laboratory measurement over the first calendar quarter of the NIED Study cohort were used in this study.

The following additional tests were performed from in the first blood sample of the base calendar quarter: Serum high sensitivity CRP was measured by a turbidometric immunoassay in which a serum sample is mixed with latex beads coated with anti-human CRP antibodies forming an insoluble aggregate (manufacturer: WPCI, Osaka, Japan, unit: mg/L, normal range: <3.0 mg/L).[43, 44] IL-6 and tumor necrosis factor alpha (TNF-α) were measured with immunoassay kits based on a solid phase sandwich ELISA using recombinant human IL-6 and TNF-α (manufacturer: R&D Systems, Minneapolis, MN; units: pg/ml; normal range: IL-6: <9.9 pg/ml, TNF-α: <4.7 pg/ml).[45-47] CRP, TNF-alpha, IL-1 and IL-6 were measured in the General Clinical Research Center Laboratories of Harbor-UCLA Medical Center. Serum transthyretin (prealbumin) was measured using immunoprecipitin analysis. Plasma total homocysteine concentrations were determined by high-performance liquid chromatography in the Harbor-UCLA Clinical Laboratories.

Statistical Methods

Chi-square test and linear regression analysis were employed to examine the differences of proportion and trends of quantitative variables between the three groups of serum PTH level (i.e. <150, 150–300, ≥300 pg/ml), respectively. Multivariate logistic regression analyses were performed to obtain unadjusted and case-mix adjusted odds ratios (OR) of having PTH <150 pg/ml in the 460 patients with PTH <300 pg/ml. To examine the bearing of inflammation on low PTH (i.e. <150 pg/ml), ORs of having low PTH was examined in patients with IL-6 ≥5 vs. IL-6 <5 pg/ml, with CRP ≥15 vs. CRP <15 mg/l, and with TNF-α ≥6 vs. <6 pg/ml. Then, in Model 1, ORs were adjusted for age, gender, race/ethnicity, diabetes, log vintage, primary insurance, modified Charlson comorbidity score, dialysis dose (Kt/v). ORs derived from Model 2 were adjusted for the variables of the Model 1 and serum albumin, creatinine, phosphorus, total iron binding capacity, bicarbonate, lymphocyte percentage, body mass index, and logarithm of paricalcitol dose. To calculate the relative risks of death in different groups of serum PTH, hazard ratios (HR) were obtained using Cox proportional hazard models, assuming those with PTH between 300 and 600 pg/ml as reference group, before and after controlling for the relevant covariates. Plots of log [-log (survival rate)] against log (survival time) were performed to establish the validity of the proportionality assumption. Fiducial limits are given as mean±SD (standard deviation); odds

ratios and risk ratios include 95% confidence interval (CI) levels. A *p*-value <0.05 or a 95% CI that did not span 1.0 was considered to be statistically significant. Descriptive and multivariate statistics were carried out with the statistical software "Stata version 10.0" (Stata Corporation, College Station, Texas)

Results

The 748 MHD patients were 53.5±18.6 years old (mean±SD); 47% of patients (n=351) were women, 50% (n=373) Hispanic, 32% (n=239) African-American and 55% (n=413) diabetic. The mean dialysis vintage was 32±34 months (median: 21 months, inter-quartile range: 8–45 months). The average baseline serum intact PTH in the 748 MHD patients was 350±351 pg/ml (median: 247, minimum: 2, maximum: 2680, inter-quartile range: 159-408 ng/mL). Table 1 shows relevant variables in the 3 groups of patients classified based on the KDOQI recommended value of serum PTH.. Patients with serum PTH <150 pg/mL were more likely to be Hispanic and less likely to be African-American and included 70% diabetics. They had higher comorbidity score, lower serum albumin level, and smaller biceps skinfold and mid-arm muscle circumference. The MIS was higher in patients with serum PTH <150 pg/mL indicating worse nutritional status. Moreover, patients with low serum PTH had received lower doses of erythropoietin and Paricalcitol (Table 1). Crude (unadjusted) mortality and transplantation rates were similar across the three PTH groups, but significantly fewer patients received the active vitamin D paricalcitol with lower PTH levels. Among 167 MHD patients who underwent additional tests in the GCRC, coronary artery calcification score, bone mineral density and total protein and calorie intakes were similar across the three PTH groups (Table 1).

In order to examine the differences across smaller ranges of serum intact PTH with more focused emphasis on low PTH ranges, we defined two smaller categories around the KDOQI-recommended lower threshold of 150 pg/ml, i.e., 100 to <150 pg/ml (borderline low) and150 to <200 pg/ml (low normal). We also subdivided the high (≥300 pg/ml) range into "moderately high" (300 to <600 pg/ml) and "very high" (≥600 pg/ml) subgroups. Hence, seven *a priori* PTH increments were defined including <100, 100-149, 150-199, 200 to 249, 250 to 299, 300 to 599 and ≥600 pg/ml. Figure 1 shows that patients with lower serum PTH concentrations had worse nutritional status including lower serum albumin and creatinine concentrations, and higher MIS. Higher PTH was associated with higher level of serum alkaline phosphatase, but in normal to lower ranges of PTH serum alkaline phosphatase did not differ substantially. Proportion of patients receiving active vitamin D (paricalcitiol) was lower across lower PTH levels. Coronary artery calcification score was not different across the PTH groups. Bone mineral density and protein or calorie intakes were not different across these PTH groups either (data not shown).

In order to examine the relative contribution of the malnutrition-inflammation complex versus bone turnover activity to low and high ranges of serum PTH, the associations of serum intact PTH (in <300 and ≥300 pg/ml ranges separately) with both MIS and serum alkaline phosphatase were examined as shown in Figure 2. The hypothetical regression model that was fitted to calculate the correlation coefficients (Table 2) was the following:

$$\mathbf{PTH} = \mathbf{MIS} + \mathbf{AlkPhos} + \mathbf{AlkPhos}^{*}\mathbf{MIS} + \text{others}$$

As shown in Figure 2 and Table 2, lower ranges of PTH (<300 pg/ml) were correlated significantly with the MIS ($r = -0.17$, $p<0.001$) but not alkaline phosphatase ($p=0.1$). Multivariate adjustment for case-mix variables did not change the trends. In this low PTH range, the inclusion of the interaction term "MIS multiplied by alkaline phosphatase" did not yield statistically significant associations ($p=0.7$). The higher ranges of serum PTH (≥300

pg/ml), on the other hand, were strongly correlated with serum alkaline phosphatase (r= +0.36, p<0.001) but not with the MIS; however, after the inclusion of the interaction term, the associations of the MIS and serum alkaline phosphatase as well as their interaction with serum PTH were all statistically significant (p<0.001), indicating the effect-modifying impact of the MIS on high PTH levels, as opposed to the more robust and overwhelming impact of MIS on low PTH levels.

We also examined the potential predictors of low PTH using logistic regression analyses. Table 3 shows that the likelihood of PTH <150 pg/ml (as compared to 150 to 300 pg/ml) was associated with non-black race, Hispanic ethnicity, diabetes mellitus and markers of protein-energy wasting including low serum albumin, creatinine, TIBC, and phosphorus values and a high MIS. Most but not all of these associations were robust to adjustment for age, gender, diabetes and other case-mix variables. A serum PTH <150 pg/ml was also associated with elevated inflammatory markers.

Over the 5 year follow-up, 228 (30%) patients died. In order to examine the underlying association of low PTH with survival, multivariate Cox regression were carried out. Figure 3 shows the hazard ratios of all-cause mortality in different categories of serum PTH. Patients with serum PTH between 100 and 200 pg/ml showed greater survival when compared to those with PTH ranged between 300 and 600 as the reference group after adjustment for age, gender, race/ethnicity, diabetes, and vintage. After additional multivariate adjustment for selected markers of malnutrition and inflammation, i.e., serum albumin, phosphorus, and logIL-6, a low serum PTH in the range of 100 to 150 pg/ml remained the robust correlate of the greatest survival (Figure 3) with a death hazard ratio of 0.52 (95% confidence interval: 0.29-0.92, p<0.001) compared to PTH in 300 to 600 pg/ml (reference group).

Discussion

In 748 MHD patients who were observed for up to 5 years in Southern California, we found that low serum PTH <150 pg/ml was more prevalent among non-Blacks, Hispanics, and diabetics. There was no association between serum PTH and coronary artery calcification score, bone mineral density or dietary protein or calorie intake. However, low PTH was associated with protein-energy wasting and inflammation, and this association appeared to overshadow and virtually nullify any possible relationship between serum PTH and alkaline phosphatase in low PTH ranges and modified it in high PTH ranges. Although crude mortality rates appeared similar across the PTH increments, after adjustment for case-mix and surrogates of malnutrition and inflammation, a moderately low serum PTH in the range of 100 to 150 pg/ml was associated with the greatest survival compared to other serum PTH levels. These findings may have important clinical implications, since they imply that a low PTH may be another facet of the malnutrition-inflammation complex in advanced CKD and that after controlling for this confounder, a moderately low PTH below the KDOQI recommended range is associated with the greatest survival.

KDOQI guidelines state that serum PTH should be maintained above 150 pg/ml in chronic dialysis patients in order to avoid adynamic bone disease.[12] However significant discrepancies may exist between the histopathologic diagnosis of adynamic bone disease and the biochemical diagnosis of “decreased PTH”.[16, 48] Notwithstanding the known histopathologic features of the adynamic bone disease, this condition might indeed be a secondary phenomenon and a consequence of the malnutrition-inflammation-complex,[16] which per se is commonly associated with increased cardiovascular disease and death in dialysis patients.[49] A recent study in 44 chronic peritoneal dialysis patients showed that low serum albumin was associated with adynamic bone.[50] In another study, the in vitro PTH secretion was suppressed by IL-6,[51] a strong pro-inflammatory cytokine that is

associated with poor outcome in maintenance dialysis patients.[52] Interleukin-1 beta (IL-1β), another pro-inflammatory cytokine, inhibits PTH secretion in cultured parathyroid tissue slices.[53] This effect may be mediated through the specific IL-1 receptors that upregulate calcium-sensing receptor mRNA leading to *apparent* low bone turnover.[53] Indeed, in the foregoing study, the inhibitory effect of IL-1β could be counteracted by the IL-1 receptor antagonist (IL-1ra),[53] indicating that the inflammation induced suppression of PTH can potentially be overcome by treatment of malnutrition-inflammation complex in individuals with CKD. Moreover, very few studies in human subjects have suggested an association between *malnutrition* and low PTH. Among over 15000 dialysis patients in Japan, Akizawa and collaborates [54] reported an increased odds ratio of low PTH (<60 pg/ml) in presence of low serum albumin and urea nitrogen concentrations. Avram and collaborates [55, 56], also, reported positive correlation between serum iPTH and serum albumin, creatinine, prealbumin and total cholesterol concentrations. Fukagawa et al [57] advanced the hypothesis that relative hypoparathyroidism reflects a state of malnutrition and contributes to the poor prognosis of dialysis patients, which may be, at least in part due to unknown mechanisms related to PTH deficiency, or from other abnormalities that suppress PTH secretion. However, even though the association between malnutrition and inflammation in CKD patients is well described, [58] we are not aware of any published report examining the role of inflammatory markers and pro-inflammatory cytokines in vivo in the presence of low PTH. To the best of our knowledge, our in vivo study is the first one to indicate an association between *malnutrition-inflammation complex* and low serum PTH in CKD patients. If our findings can be verified in additional studies, interventions that can improve hypoalbuminemia and kidney disease wasting and/or inflammation may be more promising approaches for the management of the so-called adynamic bone disease or “low PTH” rather than decreasing the dose of or withholding activated vitamin D analogs or calcimimetics.[59]

In our study, patients with a low PTH (<150 pg/ml) had higher prevalence of such known risk factors of death as older age, diabetes mellitus, malnutrition-inflammation complex, higher comorbidity score and lower or no paricalcitol dose; nevertheless, they still did not have higher crude mortality. Indeed after removing the confounding impact of the above risk factors via multivariate analyses, a greater survival in MHD patients with PTH in 100 to 150 pg/ml range was disclosed. Although recent analyses of a large national database by some of our co-authors showed the greatest survival with PTH in 200 to 300 pg/ml range,[19] the said study lacked explicit inflammatory markers, comorbidity score, or malnutrition-inflammation score to adjust for. Indeed a recent epidemiologic study in non-dialysis dependent CKD patients found that the lower the PTH the greater was the survival.[22] The U-shaped PTH-survival association found in a dialysis cohort study [19] may be due to iatrogenic factors, e.g. as a result of the guidelines that recommend withholding active vitamin D and calcimimetics when PTH is below 150 pg/ml.[12] Such guidelines-imposed strategies may contribute to increased death risk in individuals with low PTH, leaving the artificial association between low PTH and increased death risk.[16]

Measured serum PTH level may also be confounded by such non-bone related factors such as obesity [60] or pentosidine.[61] The PTH assay errors may also lead to apparently low PTH levels.[62, 63] A very recent epidemiologic study found that even among dialysis patients with an intact PTH below 150 pg/ml, a high serum alkaline phosphatase (>120 U/L) was associated with higher death risk compared to lower alkaline phosphatase levels.[64] Hence, a low serum PTH may not be a reliable indicator of adynamic bone disease since both the PTH level and its measurement are subject to a significant number of non-bone related confounders. In the present study, low serum albumin, creatinine, and TIBC, and low blood lymphocyte percentage, all being markers of malnutrition-inflammation complex, were associated with low serum PTH (Table 1 and Figure 1). The better the nutritional

status, the lesser was the odds of having a PTH <150 pg/ml was (Table 3). The PTH-nutrition association we have found may also explain as to why African American dialysis patients, who usually have a better nutritional status and greater survival [65] have relatively high PTH values.[66] Similar trends were observed between relatively low serum PTH and circulating biomarkers of inflammation, but in adjusted models they were not significant (data not shown). The MIS, a constellation of markers of malnutrition and inflammation,[30, 67] was negatively associated with low serum PTH, and this association significantly modified the expected association between serum PTH and alkaline phosphatase in high ranges of PTH. Hence, it may be speculated that malnutrition-inflammation complex plays a primary role in suppressing PTH level even in the setting of normal or high turnover bone status. Among other important findings in our study is the lack of any apparent or confounded associations between serum PTH and coronary artery calcification or bone mineral density (Figure 2). Somewhat consistent with our results a recent study by Dreschler et al [68] also found that in dialysis patients with normal hypoalbuminemia or other signs of protein-energy wasting, a low PTH was associated with greater survival, which was not observed in patients with wasting.

A potential limitation of the present study is a selection bias during enrollment. However, since the mortality in the original NIED Study cohort was less than the base population [32], it might be argued that a selection bias with such a direction generally would lead to a bias toward the null, so that without this bias, our positive results might have been even stronger. Another limitation of our study is that we did not have bone biopsy specimens to determine adynamic bone disease histologically, even though serum alkaline phosphatase and minerals were available and analyzed. Furthermore, the laboratory values examined are from the first calendar quarter of the cohort ignoring the variations over time. The study was prior to wide-spread use of calcimimetics, which usually lead to decline in PTH,[69] and we did not have type of phosphorus binder records, which may affect PTH. The strengths of our study include the moderately large sample size, long follow-up period of up to 5 years, comprehensive clinical and laboratory evaluations including body composition measures, detailed evaluation of comorbid states by the study physicians, and measuring proinflammatory cytokines. Another strength is that the subjects were selected randomly without having any prior knowledge of their inflammatory status. Finally, the same blood specimens that were utilized to measure markers of nutritional status and cytokines were also used for PTH and other blood measurements.

Conclusions

Serum intact PTH below 150 pg/ml was associated with surrogates of malnutrition-inflammation complex in a cohort of 748 MHD patients. Among the subgroup of 167 randomly selected MHD patients who also underwent EBCT and DEXA serum PTH was associated neither with coronary artery calcification nor with bone mineral density. Despite the higher prevalence of death risk markers in patients with low PTH, patients with a serum intact PTH between 100 and 150 p/ml had greater chance of survival in comparison to those with higher or lower PTH concentrations after adjustment for case-mix, paricalcitol administration and malnutrition-inflammation surrogates. These findings lead us to speculate that relatively low PTH may be another facet of the malnutrition-inflammation complex in MHD patients and that withholding active vitamin D or calcimimetics may not be warranted in moderately low PTH levels, e.g., in 100 to 200 pg/ml range. Appropriate interventions aiming at improving nutritional and inflammatory status of CKD patients may help implement better management strategies for low PTH and presumed adynamic bone disease. Additional prospective observational and interventional studies are needed to carefully examine the accuracy of our findings and the nature of the associations between malnutrition-inflammation complex, kidney bone disease and survival in CKD patients.

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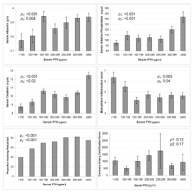

Figure 1.
Mean (± Standard error of mean) of some markers of nutrition, serum alkaline phosphatase, Paricalcitol dose and malnutrition-inflammation score in 748 maintenance hemodialysis patients: <100 (n=89), 100–149 (n=83), 150–199 (n=108), 200–249 (n=97), 250–299 (n=83), 300–600 (n=188), ≥600 (n=100),
FOOTNOTE:
P for trend: P_1: Unadjusted, P_2: Case-mix adjusted
Case-mix variables: age, gender, race/ethnicity, diabetes, log vintage, primary insurance (medicare), modified Charlson comorbidity score, dialysis dose (kt/v)

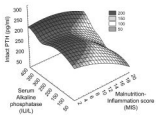

Figure 2.
Relationship between serum intact PTH as the dependent variable and serum alkaline phosphatase and malnutrition-inflammation score (MIS) as independent variables in two mutually exclusive ranges of serum PTH, i.e., <300 pg/ml (upper panel) vs. ≥300 pg/ml (lower panel).

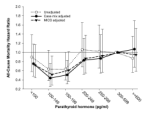

Figure 3.
Hazard ratios of all-cause mortality for serum parathyroid hormone (PTH) in 748 maintenance hemodialysis patients (9/2001–1/2007)
Case mix: Adjusted for age, gender, race/ethnicity, diabetes, and vintage (≥1 y. vs. <1 y.)
MICS: Adjusted for case mix variables and serum albumin, phosphorus, and Log interleukin-6

Table 1

Baseline demographic, clinical, and laboratory variables according to the three *a priori* selected groups of serum PTH (pg/ml) in 748 MHD patients[1]

Variable	<150 (n=172)	150 to <300 (n=288)	≥300 (n=288)	*P* trend
Demographics & Comorbidity				
Age (years)	57±14	55±15	50±15	<0.001
Women (%)	45	45	50	0.3
Race: % African-American	17	32	41	<0.001
Ethnicity: % Hispanic	60	51	42	<0.001
Diabetes mellitus (%)	70	57	44	<0.001
Modified Charlson comorbidity score	2.2±1.5	2.0±1.6	1.6±1.6	<0.001
Primary insurance: % Medicare	48	49	56	0.12
Coronary artery calcium score[3]	786±1062	1323±2653	794±1391	>0.9
Malnutrition-inflammation score	5.9±4.5	4.5±3.2	4.7±3.4	0.002
Crude mortality (%)	32	30	31	0.9
Body composition				
Triceps skinfold (mm)	17.2±9.2	17.1±9.8	18.0±10.4	0.4
Biceps skinfold (mm)	8.8±6.5	9.9±8.6	10.6±8.0	0.03
Mid-arm muscle circumference (cm)	25.2±3.7	25.9±4.3	26.5±4.9	0.005
Near infrared measured body fat (%)	26.1±10.1	26.3±10.4	26.9±11.8	0.4
Total calorie intake (Kcal/day) [3]	1649±563	1611±624	1736±710	0.5
Total protein intake (gr/day) [3]	71.0±27.7	65.2±26.8	68.1±29.1	0.7
Total bone mineral density (gr/cm^2) [3]	1.08±0.14	1.05±0.11	1.05±0.12	0.23
Hemodialysis treatment measures				
Dialysis vintage (months)	26.4±30.1	25.1±31.6	39.1±37.6	<0.001
Dialysis dose (Kt/*V* single pool)	1.61±0.30	1.62±0.30	1.58±0.31	0.14
nPNA or nPCR ($g.kg^{-1}.day^{-1}$)	1.07±0.25	1.06±0.22	1.07±0.23	0.8
Active Vitamin D				
Paricalcitol dose (mcg/month)*	27±22	38±29	62±56	<0.001
Paricalcitol administration*	48%	74%	80%	<0.001
Biochemical measurements				
Serum Albumin (g/dl)	3.78±0.44	3.90±0.36	3.93±0.32	<0.001
transthyretin (prealbumin) (mg/dl)	27.3±10.6	28.4±9.6	28.7±9.2	0.15
creatinine (mg/dl)	9.0±3.2	10.3±3.0	11.1±3.4	<0.001
calcium (mg/dl)	9.3±0.7	9.3±0.6	9.4±0.7	0.08
phosphorus (mg/dl)	5.1±1.3	5.6±1.3	6.5±1.5	<0.001
alkaline phosphatasae (mg/dl)	102±53	104±52	129±86	<0.001
total homocysteine (μmol/l)	21.6±7.1	23.4±10.7	25.8±13.0	<0.001
C-reactive protein (mg/l)	6.1±6.5	5.2±5.6	6.1±8.3	0.7
IL-6 (pg/ml)	18.6±36.9	16.7±49.3	17.6±47.2	0.9
TNF-α (pg/ml)	9.2±12.4	9.4±14.2	8.7±10.3	0.7

Variable	<150 (n=172)	150 to <300 (n=288)	≥300 (n=288)	*P* trend
Blood hemoglobin (g/dl)	12.0±1.0	12.1±0.9	12.0±1.0	0.4
WBC (×1000 cell/μl)	7.3±1.9	7.3±2.1	7.1±2.0	0.3
lymphocyte (% of total WBC)	20.8±6.8	23.0±8.5	23.4±8.5	0.002

[1] Kt/*V*, dialysis dose; nPCR, normalized protein catabolic rate; IL-6, Interleukin 6; TNF-α, Tumor necrosis factor-α

[2] All values are presented as Mean ± SD or percentages

P-values for dialysis dose (vintage), ferritin, CRP, IL-6, and TNF-α are based on the logarithmic values of these measures.

[3] The number of patients in NIED substudy in each group of iPTH is: 48, 67, and 52 for <150, 150 to <300, ≥300, respectively

Table 2

Examining statistical correlations between serum intact PTH (divided into two mutually exclusive ranges of <300 pg/ml and ≥300 pg/ml) and the MIS and serum alkaline phosphatase (AlkPhos) based on the hypothetical regression model:

$$\mathbf{PTH} = \mathbf{MIS} + \mathbf{AlkPhos} + \mathbf{AlkPhos}^{*}\mathbf{MIS} + \text{others}$$

The "adjusted" models also include age, sex, race, dialysis vintage, and modified Charlson comorbidity score as "others" in the regression model.

	PTH <300 pg/ml (n=460)		**PTH ≥300 pg/ml (n=288)**	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**
Without interaction				
MIS	**−0.17** (p<0.001)	**−0.16** (p=0.002)	−0.01 (p=0.9)	+0.05 (p=0.4)
AlkPhos	+0.07 (p=0.1)	+0.11 (p=0.1)	**+0.36** (p<0001)	**+0.35** (p<0.001)
With interaction				
MIS	−0.09 (p=0.07)	−0.09 (p=0.08)	**+0.15** (p=0.02)	**+0.21** (p=0.001)
AlkPhos	+0.03 (p=0.5)	+0.03 (p=0.6)	**+0.37** (p<0.001)	**+0.38** (p<0.001)
MIS*AlkPhos	+0.01 (p=0.9)	+0.02 (p=0.7)	**−0.20** (p<0.001)	**−0.24** (p<0.001)

Table 3

Odds ratios (and 95% CI) of having a low PTH level <150, (n=172) vs. target range PTH (150-300, n=288)[1]

Variable	Unadjusted	Case-Mix adjusted
Demographic		
Age (each 10 year ↑)	1.09 (0.96–1.25)	1.05 (0.90–1.22)
Women (vs. men)	0.97 (0.66–1.42)	1.06 (0.69–1.64)
Race: Non-Blacks vs. Blacks	**2.33 (1.49–3.70)** ***	**2.38 (1.41–2.38)** **
Ethnicity: Hispanic (vs. others)	**1.47 (1.00–2.15)** *	1.49 (0.98–2.26)
Diabetes mellitus (vs. no DM)	**1.77 (1.18–2.64)** **	1.77 (0.99–3.15)
Modified Charlson comorbidity score (each 1 unit ↑)	1.11 (0.98–1.24)	0.98 (0.83–1.17)
Dialysis vintage <6 mo vs. 6-12 mo.	1.08 (0.58–2.02)	1.18 (0.60–2.31)
Nutritional Status and Body composition		
Malnutrition-inflammation score (each 5 ↑)	**1.68 (1.29–2.18)** ***	**1.63 (1.10–2.22)** **
Malnutrition-inflammation score ≥5	**1.62 (1.10–2.40)** *	1.52 (0.96–2.40)
Mid-arm muscle circumference (each 1 cm ↑)	0.97 (0.91–1.01)	0.95 (0.90–1.00)
Near infrared measured body fat (each 1% ↑)	1.00 (0.98–1.02)	0.98 (0.95–1.01)
Hemodialysis treatment measures		
Dialysis dose (each 1 unit Kt/*V* sp ↑)	0.92 (0.48–1.74)	1.01 (0.99-1.02)
nPNA or nPCR (each 0.1 $g.kg^{-1}.day^{-1}$ ↑)	1.01 (0.93–1.09)	0.97 (0.89–1.07)
Paricalcitol dose (each 10 mg/mo ↑)	**0.83 (0.73–0.94)** **	**0.85 (0.75–0.98)** *
Biochemical measurements		
Serum Albumin (each 0.1 g/dl ↓)	**1.08 (1.02–1.12)** **	**1.08 (1.01–1.14)** *
creatinine (each 1 mg/dl ↓)	**1.14 (1.06–1.20)** ***	**1.11 (1.03–1.22)** **
Total iron binding capacity (each 10 mg/dL ↓)	**1.09 (1.03–1.14)** **	**1.09 (1.03–1.16)** **
calcium (each 1 mg/dl ↑)	1.04 (0.77–1.39)	1.13 (0.81–1.58)
phosphorus (each 1 mg/dl ↓)	**1.39 (1.19–1.64)** ***	**1.41 (1.18–1.67)** ***
phosphorus <3.5 vs. (≥3.5 mg/dl)	**2.75 (1.16-6.49)** *	**3.13 (1.24-7.94)** *
Alkaline phosphasae (each 10 mg/dl ↑)	0.99 (0.96–1.03)	1.00 (0.99–1.00)
TNF-α ≥6 (vs. <6 pg/ml)	**1.56 (1.06-2.30)** *	**1.64 (1.07-2.51)** *
CRP ≥15 (vs. <15 mg/l)	**1.99 (1.02-3.86)** *	1.85 (0.90-3.77)
IL-6 ≥ 5 (vs. <5 pg/ml)	1.44 (0.95-2.18)	1.50 (0.95-2.37)
Blood hemoglobin (each 1 g/dl ↑)	0.87 (0.71–1.07)	0.86 (0.69–1.08)
WBC (each 1000 cell/μl ↑)	1.00 (0.91–1.10)	0.96 (0.86–1.06)
lymphocyte (each 1 % ↑)	**0.96 (0.93–0.99)** **	0.97 (0.95–1.0)

CRP, C-reactive protein; IL-6, Interleukin 6; TNF-α, Tumor necrosis factor-α

Case-mix variables: age, gender, race/ethnicity, diabetes, log vintage, primary insurance (medicare), modified Charlson comorbidity score, dialysis dose (kt/v)

* *p*=0.01 to 0.05

** *p*=0.001 to 0.01

*** $p<0.001$