Serum β-Crosslaps as Predictor of Long-term Parathyroid Hormone Levels in Hemodialysis Patients

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Background and Aims: Parathyroid hormone (PTH) measurements in hemodialysis (HD) patients are routinely performed every 3 to 6 months of therapy, which are adjusted in accordance with PTH. However, recent evidences show very high PTH biological variability. The aim of our study was to evaluate the role of serum β-crosslap (CTX), a validated marker of bone resorption, as indicator of PTH maintenance at different time intervals.

Methods: Forty-six HD patients fulfilled the inclusion criteria (HD age of more than 21 months and 7 PTH measurements for the last 21 months) for this retrospective cohort study and were enrolled. Data of the backward quarter PTH values for the last 21 months were collected from clinical records, and a single CTX was measured.

To evaluate the relationship between CTX value and the maintenance of PTH in the short-term and long-term, 7 time intervals (3, 6, 9, 12, 15, 18, and 21 months) were stated and the mean value of PTH was measured within each interval and calculated for every patient.

Results: We found the following: (1) positive correlation between mean PTH in each time interval and β-crosslaps with a progressive increase of the correlation coefficient (highest value for the 12- and 21-month intervals); (2) significant differences between tertiles of β-crosslaps at 6-, 9-, 12-, 15-, 18-, and 21-month intervals, with a progressively growing value of the test coefficient; and (3) after the computation of receiver operating characteristic curves, β-crosslaps showed to significantly estimate threshold PTH values with the highest areas under the curves (AUCs; AUC, 0.763; 95% confidence interval, 0.625–0.901 for <150 pg/mL of PTH; AUC, 0.774; 95% confidence interval, 0.614–0.934 for >300 pg/mL of PTH) and best value of both sensitivity and specificity at the 12-month time interval (82% and 72% for <150 pg/mL of PTH; 78% and 79% for >300 pg/mL of PTH).

Conclusions: In HD patients, β-crosslaps have a potential ability to best estimate backward PTH into 12 months of interval.

Key Words: parathyroid hormone, serum crosslaps, hemodialysis

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The term *chronic kidney disease–mineral and bone disorder* (CKD-MBD) is routinely used since 2006 to describe systemic disorders of mineral and bone metabolism as a consequence of renal disease.[1]

Surrogate bone chemical markers, such as serum calcium (Ca^{2+}), phosphate (PO_4^{-}), alkaline phosphatase (ALP), and, mainly, plasma levels of intact parathyroid hormone (PTH), are commonly used in the management of CKD-MBD in clinical settings.[2,3] Usually, single PTH measurements are performed every 3 to 6 months and patients are treated in accordance with well-established thresholds of PTH levels, whereas recent evidences show a very high biological variability of PTH in hemodialysis (HD) patients.[4,5]

On this basis, it has been proposed that absolute measurements of PTH at determined time points are not the ideal tool to modulate therapy but would be better to evaluate PTH variability over time or search for new surrogate markers of variability.

The aim of our study was to evaluate the ability of serum β-crosslaps (CTX), the cross-linked C-terminal telopeptides of type I collagen, a validated marker of bone resorption,[6] to estimate backward PTH levels in accordance with different time intervals in a cohort of HD patients. Furthermore, we aimed to investigate the potential role of CTX as indicator of a target level of PTH maintenance.

PATIENTS AND METHODS

Patient Selection and Clinical Parameters

This retrospective cohort study was performed in accordance with the guidelines of good clinical practice in accordance with the Declaration of Helsinki and with the approval of the local medical ethics committee. Written informed consent was obtained from all patients before starting the study.

Of the 98 patients recruited from the 2 HD units of Catanzaro, Italy (Pugliese-Ciaccio Hospital and Mater Domini University Hospital), 46 patients fulfilled the inclusion criteria. Admission criteria included HD age of more than 21 months and PTH values recorded every 3 months for the last 21 months. Patients with a history of parathyroidectomy or renal transplantation, clinical instability (cardiovascular events, intermittent inflammatory illnesses, malnutrition, bone fractures for the last 24 months), current or recent history of malignancy, thyroid disease, infectious disease, or cholestatic liver disease were not included.

Table 1 shows the main demographic, clinical, and laboratory characteristics of the enrolled patients. No racial differences were present in the population. All patients were receiving regular, standard (4-hour, thrice-a-week) renal replacement treatment with standard bicarbonate dialysis (Na^{+}, 138 mmol/L; HCO_3^{-}, 35 mmol/L; K^{+}, 1.5 mmol/L; Ca^{+2}, 1.25 mmol/L; and Mg^{+2}, 0.75 mmol/L) using synthetic biocompatible membranes. The surface area of dialyzers ranged between 1.3 and 1.8 m^2 and was decided in accordance with the clinical and physical characteristics of the patients. All patients had been dry-weight stable for the last 3 months, had achieved a normotensive edema-free state, and had an adequate dialysis delivery (dialysis adequacy index, Q3.6 per week). All patients were treated as recommended by the current Kidney Disease Outcomes Quality Initiative (KDOQI) Clinical Practice Guidelines for renal bone disease to achieve the advised ranges of PTH, Ca^{+2}, PO_4^{-},

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TABLE 1. Population's Main Characteristics and Intact PTH Value Measured in the Same Occasion of β-Crosslaps (Last Month) and 3, 6, 9, 12, 15, 18, and 21 Months Before

Parameters	Value
n	46
Sex (male/female)	10/36
Dialysis vintage, mo	154 (94)
Age, y	63 (13.7)
Body mass index, kg/m^2	28.3 (5.0)
Systolic blood pressure, mm Hg	124 (28)
Diastolic blood pressure, mm Hg	64 (7)
Albumin, g/dL	3.8 (0.5)
Hemoglobin, g/dL	11.8 (1.9)
Total cholesterol, mg/dL	160 (38)
C-reactive protein, mg/L	8.0 (7.0–11.3)
Ferritin, ng/mL	159 (49–240)
Kt/V	1.30 (0.78)
Calcium, mg/dL	9.2 (0.6)
Phosphate, mg/dL	4.1 (2.1)
ALP, IU/mL	93 (36)
PTH, pg/mL	
Last month	254 (161–319)
Third month	200 (121–278)
Sixth month	223 (94–343)
Ninth month	201 (130–354)
Twelfth month	296 (205–394)
Fifteenth month	184 (88–267)
Eighteenth month	227 (122–338)
Twenty-first month	235 (110–362)
Serum beta-crosslaps, ng/mL	1.9 (1.4–2.1)
PTH, %	
Twelve-month CV	35 (27–42)
Twenty-one–month CV	37 (29–50)

Continuous variables are represented as mean (SD) or median (interquartile range) as appropriate.

ALP, and the calcium-phosphate product.[7] During the long period of observation (21-month period), the patients were treated, following routinely guidelines, to maintain PTH in determined KDOQI ranges through the administration of drugs such as cinacalcet (38%), vitamin D (75%), phosphate binders (92%), and others (6%).

Laboratory Measurements

Data of the backward quarter PTH values for the last 21 months were collected from clinical records. Parathyroid hormone measurements were carried out uniformly in all patients: fasting was done in the morning and before starting a midweek HD session after a short interdialytic period. Parathyroid hormone tests were performed using the ADVIA Centaur automated immunoassays (Siemens Healthcare, Erlangen, Germany) in a central laboratory.

After the collection of all PTH data, a fasting blood sample was taken in a midweek interdialytic day via a 20-gauge butterfly needle inserted into the forearm vein and was promptly brought to the laboratory for centrifugation at 4000 rpm for 10 minutes at 4°C and storage at −20°C. The degradation products of C-terminal telopeptides of type I collagen (CTX) were measured, in a fasting state, within 1 month using the Serum CrossLaps enzyme-linked immunosorbent assay test (Immunodiagnostic Systems Ltd, Boldon, United Kingdom). Contemporarily, PTH and other conventional biochemical parameters were measured.[8] ELISA test was repeated twice for each serum sample, and the average value of the 2 measurements was used for the statistical analyses.

Statistical Analysis

Continuous variables are expressed as means (SDs) or medians and interquartile range, as appropriate. Comparisons between continuous data were performed using Spearman bivariate correlation test.

Friedman test was used to evaluate the intraindividual variability of PTH measured in the quarter points.

To better assess the difference of PTH levels according to different degrees of CTX increase, the population was divided into tertiles of the in-study marker, CTX (first group, 0.7–1.4 ng/mL; second group, 1.4–2.2 ng/mL; third group, >2.2 ng/mL). A Kruskal-Wallis test was performed and a post hoc test was then applied to analyze the differences between groups.

To evaluate the relationship between CTX value and the maintenance of PTH in the short-term and long-term, 7 time intervals (3, 6, 9, 12, 15, 18, and 21 months) were individuated and the mean of PTH was measured within each interval and calculated for every patient (Fig. 1).

Finally, receiver operating characteristic (ROC) curves were drawn and the areas under the curves (AUCs) were calculated to investigate the potential role of CTX as indicator of a target level of PTH maintenance (<150 or >300 pg/mL, according to the KDOQI guidelines[9]) during the in-study time intervals.

Statistical analysis was performed using IBM Statistical Package for the Social Sciences Statistics 20 and the level of significance was set at P values < 0.05.

RESULTS

Relationship Between PTH and CTX in the Whole Study Cohort

For each participant, the average of quarterly PTH determinations obtained in specific time intervals of observation (up to 21 months before CTX measurement) was calculated, and the median values are shown in Table 2. We preliminarily verified the correlation between the PTH value at each time interval and the CTX in the whole study cohort, observing a positive correlation (Table 2). Serum β-crosslap was repeated in duplicates on the same sample showing an intra-assay coefficient of variation (CV) of 1.1% to 4.4%. Of note, this was

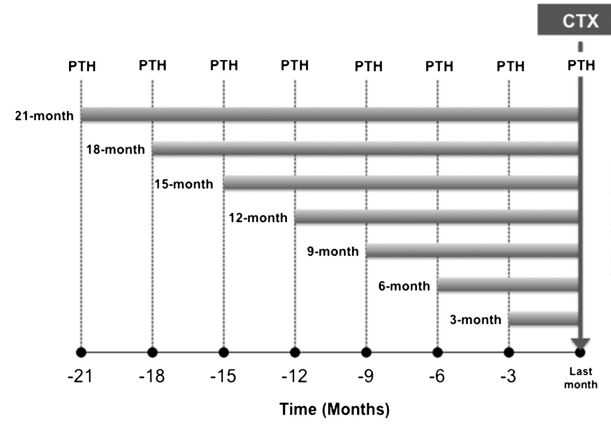

FIGURE 1. Graphical representation of the study methodology.

TABLE 2. Median and Interquartile Range of PTH Value (Expressed as Picogram per Milliliter) Measured in the Same Occasion of CTX (Last Month) and of the Average PTH Levels Maintained Within the In-Study Intervals and Their Correlation With CTX

Interval, mo	PTH (IQR)	*R*	*P*
Last month	254 (161–319)	0.231	0.189
3	232 (134–277)	0.322	0.035
6	213 (116–289)	0.351	0.019
9	210 (111–285)	0.405	0.005
12	217 (112–321)	0.429	0.003
15	206 (110–323)	0.418	0.004
18	204 (107–314)	0.421	0.004
21	210 (109–309)	0.428	0.003

IQR indicates interquartile range; *P*, correlation level of significance; *R*, Spearman correlation coefficient.

characterized by a progressive increase of the correlation coefficient, which reached the highest value when the 12- and 21-month intervals were evaluated. On the contrary, no correlation was found between CTX values and PTH measured in the same month ("last month" in Table 2).

Relationship Between PTH and the Degree of CTX Increase

Starting from the results of the bivariate correlation analysis, we decided to better assess the correlation between PTH and the degree of CTX increase. Considering that no patient in the study cohort showed CTX values below or within the reference range (0.2–0.7 ng/mL[10]), we divided the population into 3 groups according to the tertiles of CTX values that, in turn, corresponded to a CTX increase of up to 2, from 2 to 3, and more than 3 folds of the upper reference level, respectively. Then, we analyzed the differences between groups in the distributions of the in-study PTH values, finding significant trends at 6, 9, 12, 15, 18, and 21-month time intervals, with a progressively growing value of the test coefficient (Table 3). Again, we did not find differences between the CTX value groups and the last measurement of PTH. Of note, we also found no significant differences between the CTX value groups in the distribution of the average PTH measured within the 3-month time interval (Table 3; PTH values measured in the "last month" and 3 months before the CTX analysis, Fig. 1).

Post hoc test revealed that the most significant differences were found between the first and the third group for all considered time intervals.

Relationship Between the Variability of PTH and the Mineral Metabolism Markers

We found a significant intraindividual variation of PTH for the 12- and 21-month time intervals ($P = 0.006$ for both). Therefore, we calculated the percent CV (%CV; SD divided by the mean × 100,[11]) of PTH measured for 12 and 21 months to assess the association between the degree of PTH variability and CTX, but we found no correlation. Moreover, to exclude any association between CTX and PTH in specific population clusters characterized by low or high %CV of PTH, we allocated the population into 3 groups according to tertiles of PTH %CV. For a 12-month time interval, %CV in the groups varied as follows: first group, less than 27%; second group, between 27% and 42%; and third group, higher than 42%. For a 21-month time interval, the %CV groups were as follows: first group, less than 29%; second group, between 29% and 50%; and third group, higher than 50%. Again, we could not find any correlation between the CTX values and the intraindividual PTH %CV ($P = 0.705$ and 0.603 for PTH %CV for 12 and 21 months, respectively; Fig. 2).

ROC Curve Analysis to Discriminate Out-of-Target PTH Levels

Starting from the previously described results, we hypothesized that CTX could predict PTH levels under or over specific target levels (namely, <150 or >300 pg/mL, as recommended by the KDOQI guidelines). Thus, we performed ROC curve analyses, taking into consideration every time interval, which significantly correlated with CTX in the last analysis. Serum β-crosslaps had a good accuracy in predicting low PTH value of less than 150 pg/mL in all the considered time frames and high PTH value of greater than 300 pg/mL for the 9-, 12-, 15-, 18-, and 21-month time intervals (Tables 4, 5). Both the highest sensitivity and specificity values were found for a CTX cutoff value of 1.8 ng/mL for PTH of less than 150 ng/mL and a CTX cutoff value of 2.2 ng/mL for PTH of greater than 300 pg/mL for all significant ROC curves. Finally, we found the best CTX AUC value, with both high sensitivity and specificity, for the 12-month time interval (Tables 4, 5; Fig. 3, A and B). Nevertheless,

TABLE 3. Kruskal-Wallis Test for Each Considered Time Interval After Division of the Population Into Groups According to Tertiles of CTX Value

			Post hoc Test (p)		
Interval, mo	H	*P*	First vs Second	First vs Third	Second vs Third
Last month	3.523	0.172	—	—	—
3	4.803	0.076	—	—	—
6	6.570	0.037	0.935	0.035	0.023
9	8.412	0.015	0.750	0.009	0.018
12	10.198	0.006	0.836	0.005	0.007
15	10.542	0.005	0.829	0.005	0.007
18	11.047	0.004	0.896	0.004	0.004
21	11.213	0.004	0.863	0.003	0.004

First group: n = 14; CTX, <1.4 ng/mL. Second group: n = 16; CTX, ≥1.4 and ≤2.2 ng/mL. Third group: n = 16; CTX >2.2 ng/mL.

H indicates Kruskal-Wallis test coefficient; *P*, level of significance for trend, Kruskal-Wallis test; p, level of significance, post hoc test.

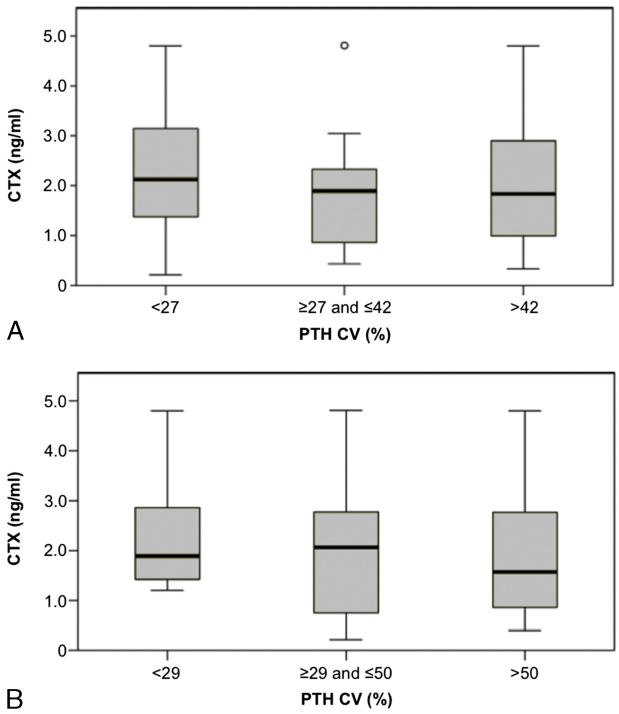

FIGURE 2. Distribution of CTX values according to groups of %CV of PTH relative to the 12- (A) and 21-month (B) time intervals.

analysis regarding the analyzed relationship between PTH and CTX was found to be independent from the pharmacological therapy received by the study population.

DISCUSSION

In our study, the main finding was the ability of a single CTX measurement to estimate, in a cohort of HD patients, average backward PTH levels into different time intervals and with the best correlation at 12- and 21-month time intervals. This suggests, apart from the limits due to a retrospective design of our study and to a small sample size of the cohort, a potential role of CTX as indicator of PTH level maintenance at different time intervals in HD patients.

Serum β-crosslap belongs to small fragments shed into the bloodstream during the renewal of the bone matrix throughout the skeleton from type I collagen degradation.

Serum β-crosslap is a validated marker of bone resorption used to monitor during therapy with teriparatide, a recombinant protein encompassing the first 34 amino acids of human PTH and the only anabolic agent approved by the Food and Drug Administration for the treatment of osteoporosis.[6] In fact, the intermittent administration of PTH (ie, daily injections of teriparatide) activates osteoblasts more than osteoclasts, stimulating new bone formation and increasing bone mass density with a positive response in bone formation and bone resorption markers in treatment responders.[12,13]

Serum β-crosslap, with other markers, was recommended by the International Osteoporosis Foundation/International Federation of Clinical Chemistry and Laboratory Medicine (IOF-IFCC) Bone Marker Standards Working Group to monitor antiresorptive therapies in postmenopausal osteoporotic women and in osteopenic patients.[6] In addition, CTX is related to the monitoring of PTH analogs and positively correlates with improvements in dynamic bone parameters measured after 24 months of treatment.[14]

Above all, CTX raised our interest because it is also a potential marker of bone resorption in renal bone disease.[15]

Parathyroid hormone, as a surrogate marker of bone turnover, showed several limits because of its consistent biological variability. Garrett et al.[16] in a recent analysis regarding evidences at support of single PTH measurements for bone disease management defined *PTH* as a "tricky" hormone. In accordance with the Kidney Disease Improving Global Outcomes guidelines, Garrett et al.[16] advised to look out PTH changes over time and not simply at singular values. Lamb et al.,[17] measuring PTH twice/week for 6 weeks in HD patients, determined an incredible intraindividual CV of 72%. Hence, to estimate an individual's homeostatic PTH set point with 95% probability, they stated the need for 26 specimens over a short time.[17]

On the basis of these evidences, as postulated in the KDIGO guidelines, only extremely high PTH values from 2 to 9 folds of the upper reference limit or very low levels are correlated to real bone formation rate.[18]

On the other hand, PTH is strictly associated with an increased risk for vascular calcification, morbidity, and mortality and combines alterations in bone turnover, mineralization, and volume linear growth with extraskeletal calcifications.[1,19] Of course, PTH has a role in bone turnover but its secretion from parathyroid glands is a fast process in response to variations in ionized calcium,[20] whereas the onset of CKD-MBD is a slower process. Although systematic and sequential bone biopsy (the criterion standard for bone morphology classification) is not practicable on a large number of patients because it is painful and too invasive, new surrogate bone chemical markers could be useful to detect bone-remodelling status in chronic kidney

TABLE 4. ROC Curves Analysis Data for PTH of Less Than 150 pg/mL

Interval, mo	AUC (95% CI)	*P*	Sensitivity, %	Specificity, %
Last month	0.680 (0.520–0.900)	0.063	—	—
3	0.693 (0.530–0.880)	0.060	—	—
6	0.722 (0.570–0.874)	0.013	72	73
9	0.725 (0.579–0.872)	0.010	74	70
12	0.763 (0.625–0.901)	0.003	82	72
15	0.730 (0.584–0.876)	0.010	77	69
18	0.730 (0.584–0.876)	0.010	77	69
21	0.730 (0.584–0.876)	0.010	77	69

95% CI indicates 95% confidence interval.

TABLE 5. ROC Curves Analysis Data for PTH of Greater Than 300 pg/mL

Interval, mo	AUC (95% CI)	*P*	Sensitivity, %	Specificity, %
Last month	0.637 (0.418–0.856)	0.184	—	—
3	0.573 (0.332–0.814)	0.496	—	—
6	0.648 (0.439–0.857)	0.126	—	—
9	0.738 (0.553–0.922)	0.010	80	74
12	0.774 (0.614–0.934)	0.002	78	79
15	0.746 (0.578–0.915)	0.006	77	76
18	0.744 (0.582–0.906)	0.006	83	68
21	0.712 (0.543–0.882)	0.016	61	82

95% CI indicates 95% confidence interval.

disease (CKD) and to grade bone disease in the clinical setting. Another biomarker, the bone-specific ALP, although has a good sensitivity as a marker of bone turnover and directly reflects osteoblastic activity, raised concerns regarding cross-reaction with liver-derived ALP.[21] At the same time, other markers of bone status and remodelling were developed, but they need a validation on larger cohorts of patients or a clearer elucidation of biochemical mechanisms.

In our study, we investigated CTX, indicated as a valid alternative to bone-specific ALP for assessing bone turnover.[22] In accordance with other articles on patients with CKD, we found CTX levels greater than the reference ranges and we investigated the relationship between PTH and CTX.[23,24] It might be argued that CTX does not represent the best choice for the aim of the present study in the light of its renal excretion. However, many markers are affected by renal clearance, and consequently, new reference ranges are usually needed according to CKD stages. For example, also, PTH usually shows higher values in patients with CKD, but it is still commonly used in clinical settings and interpreted in the light of appropriate increased ranges. We suggested specific reference ranges for CTX in HD patients.

In our analysis, we retrospectively collected PTH during the previous 21 months and found a progressive increase of correlation between CTX and PTH, with highest correlation indices registered at 12- and 21-month time intervals.

The KDOQI guidelines indicate a lower cutoff value of 150 pg/mL for PTH in HD patients; this lower limit has been confirmed, more recently, using the KDIGO guidelines.[18] In our cohort of HD patients, CTX showed to significantly predict an average PTH value of below 150 pg/mL, which was recorded in the 2 previous quarters (Table 4). Interestingly, CTX showed the highest predictivity of PTH of less than 150 pg/mL when the 12-month time interval was considered, with an optimal cutoff value of 1.8 ng/mL. We similarly found that CTX measurement significantly predicted PTH levels averagely maintained greater than 300 pg/mL for a period of at least 9 months. In this case too, CTX showed to best predict average PTH maintenance when considering a time interval of 12 months, with a cutoff value of 2.2 ng/mL. More specifically, in HD patients, our analysis suggests an ideal reference range for CTX ranging between 1.8 and 2.2 ng/mL when considering the reference KDOQI PTH range.

In our cohort, we did not specifically consider a group of patients with a PTH of greater than 675 pg/mL because few participants were characterized by an average PTH level over such limit. However, the positive correlation between average PTH and CTX suggests that CTX could successfully predict average PTH values greater than 675 pg/mL, but this should be confirmed in a wider study.

The clinical relevance of our findings might be researched in a possible parallelism between the significance of CTX in

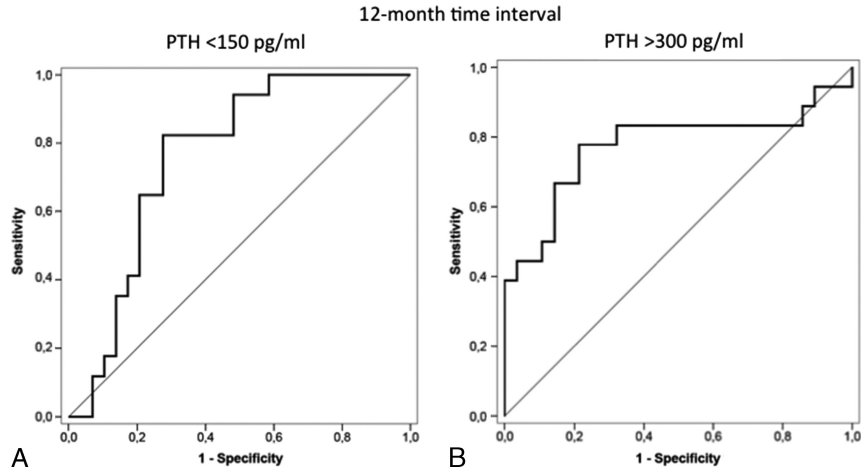

FIGURE 3. Receiver operating characteristic curve analysis of CTX for the discrimination of PTH of less than 150 pg/mL (A; AUC = 0.763; 95% confidence interval, 0.625-0.901; *P* = 0.003) and PTH of greater than 300 pg/mL (B; AUC = 0.774; 95% confidence interval, 0.614–0.934; *P* = 0.002) maintained within the 12-month time interval.

patients on chronic HD and glycosylated hemoglobin in diabetic patients. Serum β-crosslaps cannot replace the essential role of PTH to monitor the CKD-MBD in HD patients on a short-term and medium-term, just as glycosylated hemoglobin cannot replace glucose test, but would represent a parameter in the position to provide a mirror of the well-recognized and not negligible biological variations of PTH on a longer term.

In conclusion, CTX appeared as a potential indicator of average backward 12-month PTH levels, suggesting the potential feasibility of CTX besides other routinely measured mineral metabolism markers for the follow-up of CKD-MBD in HD patients.

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