Serum β-Crosslaps as Predictor of long-term Parathyroid Hormone Levels in Haemodialysis Patients

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INTRODUCTION AND AIM OF THE STUDY

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. Usually single PTH measurements are performed every 3-6 months and patients are treated according to well-established thresholds of PTH levels, while recent evidences show a very high biological variability of PTH in hemodialysis (HD) patients. On this basis, it has been proposed that absolute measurements of PTH at determined time-points is 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 reabsorption, to estimate backward PTH levels according to 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.

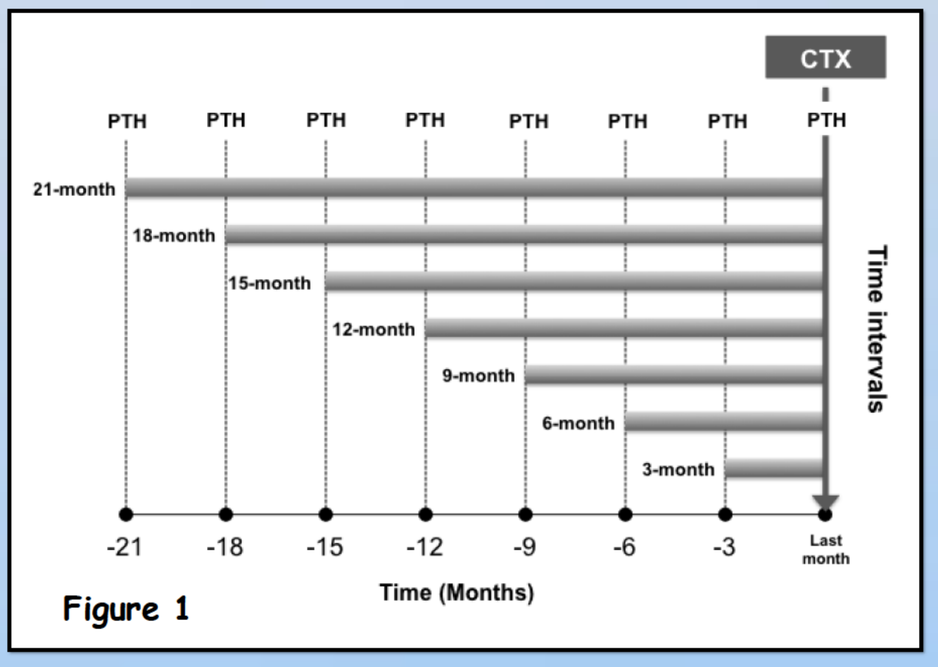

Figure 1

PATIENTS AND METHODS

Out of the 98 patients recruited from two HD units of Catanzaro (Italy) 46 fulfilled inclusion criteria. Admission criteria included HD age >21 months and PTH values recorded every three months over the last 21 months. All patients were receiving regular, standard (4-hour, thrice a week) renal replacement treatment with standard bicarbonate dialysis. All patients were treated as recommended by current K/DOQI Clinical Practice Guidelines for CKD-MBD.
Data of the backward quarter PTH values over the last 21 months were collected from clinical records. PTH measurements were carried out uniformly in all patients: fasting, in the morning and before starting a mid-week HD session after a short inter-dialytic period. The degradation products of C-terminal telopeptides of Type I collagen (CTX) was measured, in a fasting state, within one month by the Serum CrossLaps® ELISA test. In order to evaluate the relationship between CTX value and the maintenance of PTH in the short- and long-term, seven time intervals (3, 6, 9, 12, 15, 18 and 21-month) were individuated and the mean of PTH measured within each interval calculated for every patient (**Figure 1**).

RESULTS

We found: 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; 3) after computation of receiver operating characteristic (ROC) curves, β-Crosslaps showed to significantly estimate threshold PTH values with the highest AUCs (AUC=0.763, 95%CI 0.625-0.901 for PTH <150 pg/ml; AUC=0.774, 95%CI 0.614-0.934 for PTH >300 pg/ml) and best value of both sensitivity and specificity at the 12-month time interval (82 and 72% for PTH <150 pg/ml, 78 and 79% for PTH >300 pg/ml) (**Figure 2**).

Figure 2

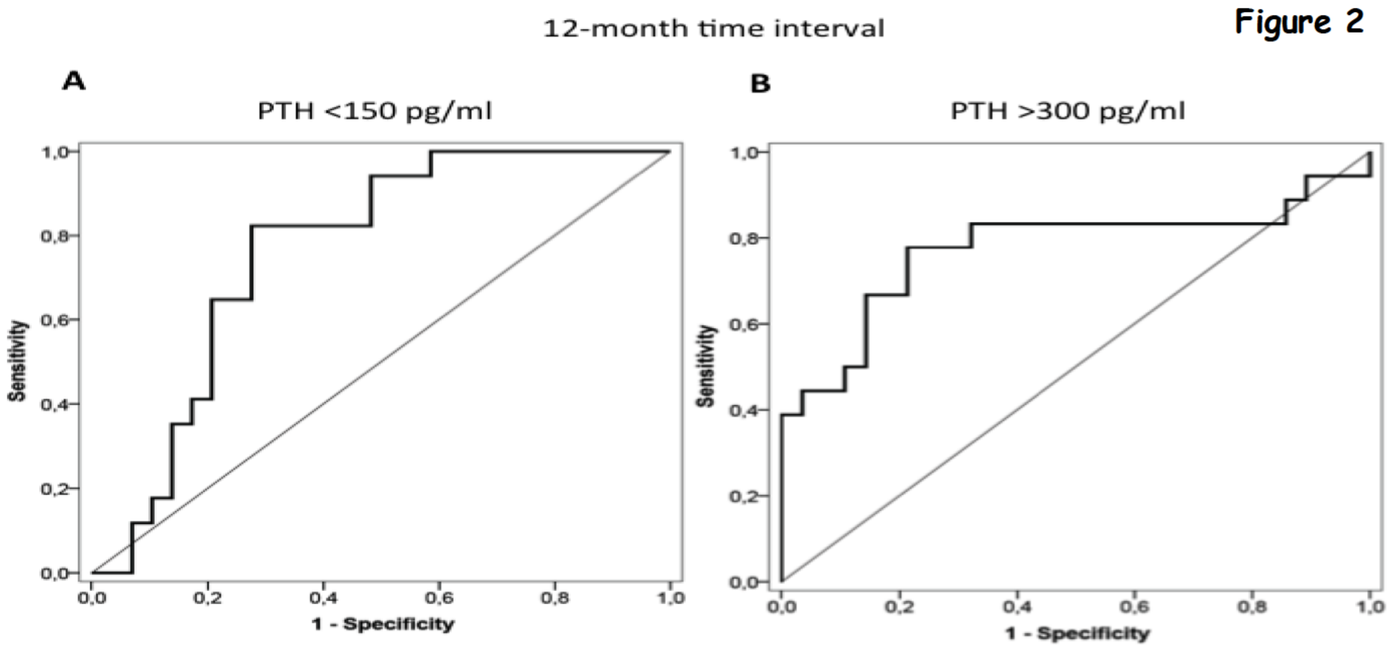

Table 2: median and interquartile range of PTH value (expressed as pg/ml) measured in the same occasion of CTX (last month) and of the average PTH levels maintained within the in-study intervals, and their correlation with CTX.

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

IQR: interquartile range. R: Spearman's correlation coefficient. *p*: correlation level of significance.

CONCLUSIONS

The clinical relevance of our findings might be researched in a possible parallelism between the significance of CTX in patients on chronic HD and glycosylated haemoglobin in diabetic patients. CTX cannot replace the essential role of PTH to monitor the CKD-MBD in HD patients on a short- and medium-term, just as glycosylated haemoglobin 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, serum 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.

Table 3: Kruskal-Wallis test for each considered time interval, after division of the population into groups according to tertiles of CTX value.

Interval	H	P	*Post-hoc* test (p)		
			1st vs 2nd	1st vs 3rd	2nd vs 3rd
Last month	3.523	0.172	--	--	--
3-month	4.803	0.076	--	--	--
6-month	6.570	**0.037**	0.935	**0.035**	**0.023**
9-month	8.412	**0.015**	0.750	**0.009**	**0.018**
12-month	10.198	**0.006**	0.836	**0.005**	**0.007**
15-month	10.542	**0.005**	0.829	**0.005**	**0.007**
18-month	11.047	**0.004**	0.896	**0.004**	**0.004**
21-month	11.213	**0.004**	0.863	**0.003**	**0.004**

1st group: n=14, CTX <1.4 ng/ml; 2nd group: n=16, CTX ≥1.4 and ≤2.2 ng/ml; 3rd group: n=16, CTX >2.2 ng/ml. H: Kruskal-Wallis test's coefficient. P: level of significance for trend, Kruskal-Wallis test. p: level of significance, *post-hoc* test.

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