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Original Paper

Bone Biopsy Results in Chronic Kidney Disease: a Single-Center Experience

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Key Words
CKD-MBD • Biomarkers • Renal osteodystrophy • Chronic renal failure • Hyperparathyroidism

Abstract
Background/Aims: Although bone histology remains the diagnostic standard in renal osteodystrophy (ROD), biomarkers are used more commonly. Data comparing bone biopsy results and biomarkers of bone metabolism remain sparse. ***Methods:*** This is a single-center retrospective analysis of bone biopsy results (105) stratified by renal function, compared with intact parathyroid hormone (iPTH), bone-specific alkaline phosphatase (BAP) and other biomarkers. We tested associations with high-turnover ostitis fibrosa (OF) and mixed uremic osteodystrophy (MUO), i.e. classes I and III according to Delling's classification. ***Results:*** 37% of patients had CKD stage 3-5 not on dialysis (CKD NOD) and 50% CKD stage 5 requiring haemodialysis (CKD 5D). iPTH was significantly higher in CKD 5D with high-turnover ROD, 26 (18) versus 8 (9) pmol/l ($p<0.001$). BAP showed no association. In CKD NOD, high-turnover ROD was associated with elevated iPTH, 32 (44) versus 8 (11) pmol/l ($p=0.001$), and BAP, 39 (32) versus 16 (7) U/l ($p=0.01$). iPTH achieved receiver operator characteristic (ROC) areas under the curve (AUC) of 0.83 ($P=0.003$) and 0.91 ($P=0.019$) for high-turnover ROD among CKD 5D and CKD NOD patients, respectively. An iPTH cutoff of 12.8 (CKD 5D) and 13.5 pmol/l (CKD NOD) reached sensitivities and specificities of 0.83, 0.91 and 1.00, 0.91, respectively. In CKD NOD, BAP achieved an AUC of 0.93 ($P=0.013$) and with a cutoff at 19.8 U/l a sensitivity and specificity of 1.00, 0.91, respectively. ***Conclusion:*** In CKD 5D patients, high-turnover ROD was associated with elevated iPTH at a low cutoff but not with BAP. The same diagnosis in CKD NOD was associated both with iPTH and BAP.

Introduction

The disturbance of mineral and bone metabolism in chronic kidney disease (CKD) can have adverse effects on various organs such as the cardiovascular system or induce soft-

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tissue calcification [1]. It may therefore not only be responsible for disabling musculoskeletal conditions but also affect cardiovascular and overall health in CKD. To better account for the importance of these disturbances, the more comprehensive term chronic kidney disease-mineral bone disorder (CKD-MBD) was coined, versus the descriptive term renal osteodystrophy (ROD) which should be exclusively used when describing bone phenotypes of CKD-MBD [2, 3].

Bone biopsy is still widely regarded as the standard in the differential diagnosis of CKD-MBD, because it provides information not only on the mineralization and turnover, but also on the microstructural competency of bone [4, 5]. Despite this, it is only infrequently performed due to its invasive nature, potential risks for complication, unavailability of experienced pathologists and cost. Instead, serum or blood biomarkers of bone turnover, most importantly parathyroid hormone and alkaline phosphatase or its tissue specific subforms, are being widely used to estimate the rate of bone turnover and to guide therapy. Although a substantial body of clinical data already exist comparing bone biopsy results with established biomarkers of bone turnover, it did not produce results that are consistent enough, as outlined below, and still leaves room for further investigation.

Von Herrath et al. in 1986 published an analysis of bone biopsy results from 113 chronically haemodialysed patients [6]. 69% showed a mixed form with predominant ostitis fibrosa and 30% pure osteoidosis and a female preponderance. Aluminum deposits were common in cases of osteoidosis and PTH level was poorly associated with histological findings. Only when patients with pure hyperosteoidosis were compared to patients with ostitis fibrosa-predominant mixed renal osteodystrophy, c-terminal intact PTH levels were higher in the latter vs. the former group (629 (729) vs. 238 (251) pmol/l, $p<0.05$), but with a wide variation of values, weakening their association with these findings. In another study by Hutchison et al., iPTH and BAP [7] both correlated with histomorphometric measures of bone turnover in 30 incident peritoneal dialysis patients, with a geometric mean iPTH of 21.6 pg/ml (2.29 pmol/l) in adynamic bone disease compared with 495.2 pg/ml (52.51 pmol/l) in severe ostitis fibrosa ($P<0.05$).

In 2005, Gal-Moscovici and Popovtzer examined 96 chronic haemodialysis patients with double tetracycline-labeled bone biopsies [8]. In 40%, ostitis fibrosa cystica and in the remaining 60%, various forms of low-turnover bone disease were observed. No associations between iPTH level with bone turnover, or with the finding of ostitis fibrosa were detected. The authors concluded that bone biopsy remains the gold-standard diagnostic tool for detecting ROD and that parathyroidectomy should not be performed based solely on the finding of elevated iPTH levels alone.

In 2008, Barreto et al. published a prospective study of 101 haemodialysis patients, of whom samples were obtained at the beginning of the study and after 1 year of follow up [9]. At entry into the study, 60% of patients had low-turnover and only 37% high-turnover bone disease. While a positive association of iPTH with bone turnover was found, rates of low-turnover bone disease were more prevalent than expected, even in patients with substantially elevated levels of iPTH, thereby weakening its association. According to the authors, the high frequency of aluminum intoxication of 41% in the study population may have biased the results.

In a much larger, KDIGO-led retrospective analysis of 492 dialysis patients from 4 countries [10], bone turnover was measured histomorphometrically. Intact PTH levels of <103.8 and >323 pg/ml (<11.0 and >34.3 pmol/l) were found to discriminate low from non-low and high from non-high bone turnover conditions, respectively, with a fair accuracy (ROC area under the curve >0.70). Regarding bone specific alkaline phosphatase (BAP), cutoff levels of <33.1 and >42.1 U/l performed similarly well [10].

In summary, additional information may be helpful to improve the interpretation of biomarkers of bone turnover with respect to the associated histologic changes found in bone. Based on this rationale, the present study was carried out.

Materials and Methods

This is a retrospective analysis of all available bone biopsy results obtained between January 1st 2008 and December 31st 2014 in our nephrology department within the realm of routine clinical care. Cases included in the analysis were from patients without known kidney disease as well as patients with chronic kidney disease of all stages who were not requiring renal replacement therapy (CKD NOD) and patients with stage 5 chronic kidney disease requiring dialysis (CKD 5D). Bone biopsies were performed without prior tetracycline labelling, from the iliac crest by trepanation under local anesthesia using a T-handle cutting cannula and with the aid of an additional extraction cannula (Trapsystem, H.S. Hospital System S.p.A., Aprilia, Italy). The biopsy specimen were immediately immersed in a buffered 4% formalin fixative solution for histopathological analysis and shipped to the osteopathology department of University Hospital Hamburg Eppendorf, Germany, for routine analysis [11, 12]. The biopsy results were reported according to Delling's classification scheme for renal osteodystrophy [11, 13]. The relationship of this classification scheme with the other two systems put forward by the Kidney Disease Outcomes Quality Initiative (K-DOQI) [14] and the Kidney Disease Improving Global Outcomes Initiative (KDIGO) [15] are shown in detail in Table 1. Pertinent clinical data including demographics, comorbid conditions, laboratory values, medications, kidney function and dialysis data were collected. Statistical analysis was performed using SPSS 14.0 (IBM Corp., Armonk, NY, USA). Data are presented in mean and standard deviation (SD), median and interquartile range (IQR) or percent, as appropriate. The nonparametric Mann Whitney U- and Fisher Exact tests were used to test for statistically significant differences due to the skewed distribution of the values. The threshold for statistical significance was set at a level of $P<0.05$. For exploration of the distribution of the data and wherever appropriate, graphical presentation was performed using box-plots or error bar graphs (data not shown). Finally, the relationship of iPTH with histological findings of high-turnover forms of ROD was explored using receiver operator characteristic curve and logistic regression analyses. iPTH and BAP were used as predictors and mixed uremic osteodystrophy (MUO or ROD type III according to Delling's classification) as well as a combination of all forms of high turnover renal osteodystrophy (i.e. ROD type I and type III according to Delling's classification) as outcome variables.

Table 1. Histological Classification Schemes for Renal Osteodystrophy (ROD) [17]; [3]; [13]; [14]. NKF K/DOQI: National Kidney Foundation Kidney Disease Outcomes Quality Initiative. KDIGO: Kidney Disease Improving Global Outcomes. TMV: Turnover-Mineralization-Volume

Delling's Criteria	K-DOQI	KDIGO (TMV)
Type 1 (ostitis fibrosa)*	Hyperparathyroid form	Turnover high Mineralization slightly impaired Volume highly variable
Type 2 (osteoidosis)*	Osteomalacia	Turnover low Mineralization substantially impaired Volume frequently increased
	Adynamic bone disease	Turnover low Mineralization not impaired Volume reduced
Type 3 (mixed)*	Mixed uremic osteodystrophy	Turnover high Mineralization substantially impaired Volume frequently increased
*Cellular activity subtypes: a (low), b (normal or slightly elevated), c (highly elevated)		

Ethics committee approval was obtained for this study prior to collection of the data which were compiled in an anonymized fashion, without patient identifiers. Due to the retrospective and anonymous nature of this analysis, the ethics committee did not require informed consent to be obtained from the patients included.

Results

A total of 109 patients were included in the analysis of which 105 had sufficient biopsy material to allow for a histologic diagnosis. Within this group, 19 patients had normal renal function, 33 had chronic kidney disease stage 3-5 not requiring dialysis (CKD NOD) and 53 had dialysis-requiring stage 5 chronic kidney disease (CKD 5D). Epidemiologic, clinical and laboratory data of the captured patient group is displayed in Table 2, stratified by renal function. There was a female preponderance among CKD NOD patients. Hypertension, bone fractures and proton pump inhibitor (PPI) use were especially prevalent among both CKD groups. As expected, average intact parathyroid hormone (iPTH) and alkaline phosphatase levels were lowest among patients with normal renal function and increasing in the CKD

NOD and CKD 5D groups. We identified no cases of renal osteodystrophy among patients with normal renal function. The most prevalent histopathologic finding among both CKD groups was high turnover mixed uremic osteodystrophy (MUO) according to the K-DOQI classification scheme corresponding to type III renal osteodystrophy (ROD III) according to Delling's classification (see Table 1 for comparison). The other form of high turnover renal osteodystrophy, ostitis fibrosa or the hyperparathyroid form according to K-DOQI, i.e. type I according to Delling's classification, was much less prevalent in this study.

Table 2. Baseline demographic, clinical and laboratory characteristics of the population studied. CKD NOD: chronic kidney disease not requiring dialysis; CKD 5D: dialysis-requiring chronic kidney disease stage V; HTN: hypertension, DM II: type 2 diabetes mellitus; CAD: coronary artery disease; PTx: history of parathyroidectomy; HPT: hyperparathyroidism; iPTH: intact parathyroid hormone; BAP: bone specific alkaline phosphatase; TSH: Thyroid stimulating hormone; PO4 phosphate; ROD Type: renal osteodystrophy type according to Delling's classification

Parameters	Normal renal function (N=19)	CKD NOD (N=33)	CKD 5D (N=53)
Age (y)	59 (11)	69 (14)	74 (10)
Weight (kg)	71 (15)	73 (17)	70 (12)
Female sex (%)	42	76	47
Creatinine (mg/dl)	0.85 (0.18)	2.03 (1.04)	6.79 (2.52)
HTN (%)	32	82	89
DM II (%)	0	33	28
CAD (%)	0	21	45
Bone fractures (%)	58	30	60
Bone pain (%)	16	27	30
Kyphosis (%)	11	9	9
PTx (%)	0	6	10
Primary HPT (%)	21	27	0
Secondary HPT (%)	11	55	93
Vitamin D deficiency (%)	42	42	13
Proton Pump Inhibitor use (%)	70	64	77
Vitamin D use (%)	50	79	98
Active Vitamin D use (%)	0	14	40
PO4 binder use (%)	0	14	72
Glucocorticoid use (%)	10	41	14
Bisphosphonate use (%)	10	7	2
iPTH (pmol/l)	8.10 (8.05)	15.02 (26.31)	19.35 (16.68)
Alkaline phosphatase (U/l)	81 (24)	102 (36)	130 (109)
BAP (U/l)	19 (8)	22 (19)	22 (13)
TSH (mU/l)	1.24 (0.75)	1.64 (1.19)	3.35 (5.27)
Calcidiol (ng/ml)	34 (16)	30 (18)	45 (17)
Calcitriol (pg/ml)	34 (16)	28 (16)	16 (13)
Calcium (mmol/l)	2.42 (0.13)	2.46 (0.35)	2.39 (0.49)
PO4 (mg/dl)	1.11 (0.14)	1.22 (0.44)	1.42 (0.40)
Albumin (g/l)	45 (6)	37 (8)	34 (7)
pH	7.40 (0.05)	7.41 (0.07)	7.40 (0.06)
Bicarbonate (mmol/l)	26.3 (1.6)	25.4 (2.3)	24.1 (4.2)
ROD Type (%)			
Ia	0	6	6
Ib	0	3	8
IIa	0	6	4
IIb	0	0	4
IIIa	0	0	0
IIIb	0	21	52

Mean (SD) levels of routine clinical blood biomarkers related to bone metabolism stratified by the finding of MUO (i.e. type III ROD) and all types of high turnover renal osteodystrophy were compared in Table 3, A and B. In the subgroup of patients with CKD 5D (Table 3, A), intact parathyroid hormone (iPTH) level was statistically significantly elevated and associated with the findings of MUO (ROD III) and all high turnover ROD (Table 3, A). In the subgroup of patients with CKD not requiring dialysis (CKD NOD; Table 3, B), intact parathyroid hormone (iPTH) level was again statistically significantly elevated and associated with the findings of MUO (ROD III) and all high turnover ROD. In addition, and importantly, BAP was also elevated and associated with both diagnosis variables in the CKD NOD group, whereas MUO (ROD III) alone but not all high turnover renal osteodystrophy (ROD I and III) was weakly associated with a lower blood pH, but not with bicarbonate in this group (Table 3, B).

In a receiver operator characteristic curve (ROC) analysis, iPTH level was strongly associated with the findings of MUO (ROD III) and all forms of high turnover ROD (ROD I and III) with areas under the curve of 0.90 and 0.83 and sensitivities and specificities in excess of 80 and 90% when choosing a cutoff level of 14.5 and 12.8 pmol/l (136.7 and 120.7 pg/ml), respectively (Table 4, A), while BAP showed no association in the subgroup of patients with CKD 5D. On the other hand, in the subgroup of CKD NOD, in addition to iPTH, BAP was also associated with the findings of MUO (ROD III) and all high turnover renal osteodystrophy (ROD I and III) with an AUC over 0.90 and sensitivities and specificities in excess of 90%, respectively (Table 4, B). Graphical plots of these ROC analyses are shown in Fig. 1.

If entered into a logistic regression model, iPTH was associated with the finding of any form of high turnover renal osteodystrophy in patients with CKD 5D, with a one-unit increase in this biomarker increasing the odds to find histological high turnover ROD by 14% (Exp. (B) 1.136; P=0.003). In the subgroup of CKD NOD, each single unit increase in iPTH was associated with an 8% increase in the odds to find high turnover ROD on histology. However, this association did not reach statistical significance (Exp. (B) 1.079; P=0.084).

Table 3. Biomarkers of bone metabolism stratified by bone histological presence of mixed uremic or all types of high turnover renal osteodystrophy in patients with dialysis-requiring CKD 5D (A) and CKD NOD (B). CKD 5D: dialysis-requiring chronic kidney disease stage 5; CKD NOD: chronic kidney disease not requiring dialysis; iPTH: intact parathyroid hormone; BAP: bone specific alkaline phosphatase

Parameter	Mixed uremic osteodystrophy			All high turnover renal osteodystrophy		
	present	absent	P	present	absent	P
A) CKD 5D						
Alkaline Phosphatase (U/l)	119 (46)	146 (156)	0.724	113 (47)	166 (176)	0.683
BAP (U/l)	20.8 (11.7)	22.7 (16.5)	0.984	19.4 (11.3)	25.7 (17.5)	0.350
iPTH (pmol/l)	28.6 (17.5)	9.2 (9.4)	<0.001	25.9 (17.7)	8.3 (8.7)	<0.001
Calcidiol (ng/ml)	47.6 (17.7)	39.7 (15.5)	0.125	45.9 (18.3)	40.6 (14.3)	0.299
Calcitriol (pg/ml)	12.4 (13.3)	16.5 (14.0)	0.340	12.4 (10.8)	17.6 (15.5)	0.422
Phosphate (mg/dl)	1.41 (0.34)	1.41 (0.47)	1.000	1.42 (0.37)	1.45 (0.48)	0.923
Calcium (mmol/l)	2.31 (0.24)	2.49 (0.67)	0.386	2.42 (0.59)	2.35 (0.67)	0.871
Albumin (g/l)	35.9 (5.7)	31.9 (7.1)	0.074	35.4 (6.6)	31.7 (6.1)	0.068
Bicarbonate (mmol/l)	23.5 (4.4)	24.7 (4.2)	0.904	24.2 (5.2)	23.6 (1.6)	0.705
pH	7.40 (0.49)	7.41 (0.08)	0.827	7.41 (0.06)	7.39 (0.06)	0.433
B) CKD NOD						
Alkaline Phosphatase (U/l)	117 (50)	97 (30)	0.333	117 (43)	93 (29)	0.169
BAP (U/l)	55.0 (43.8)	16.9 (6.7)	0.038	38.5 (31.8)	16.0 (6.9)	0.010
iPTH (pmol/l)	37.1 (50.5)	9.0 (10.4)	0.008	32.0 (43.7)	8.2 (10.5)	0.001
Calcidiol (ng/ml)	34.3 (19.4)	29.3 (17.9)	0.643	35.4 (18.5)	28.4 (17.9)	0.381
Calcitriol (pg/ml)	29.7 (14.5)	28.0 (16.4)	0.755	30.4 (16.4)	27.5 (15.9)	0.658
Phosphate (mg/dl)	1.20 (0.55)	1.22 (0.42)	0.780	1.14 (0.46)	1.25 (0.44)	0.428
Calcium (mmol/l)	2.55 (0.20)	2.44 (0.38)	0.268	2.52 (0.20)	2.44 (0.40)	0.287
Albumin (g/l)	36.3 (3.3)	37.2 (9.5)	0.304	36.7 (3.0)	37.1 (10.1)	0.240
Bicarbonate (mmol/l)	24.8 (0.8)	25.7 (2.6)	0.864	24.5 (0.9)	25.9 (2.7)	0.461
pH	7.36 (0.05)	7.44 (0.06)	0.036	7.39 (0.09)	7.43 (0.04)	0.108

Table 4. Receiver operator characteristic (ROC) curve analyses of intact PTH and bone-specific alkaline phosphatase (BAP) for their association with mixed uremic osteodystrophy (MUO), shown on the left, and all high turnover renal osteodystrophy, shown on the right, in patients with dialysis-requiring CKD 5D (A) and patients with CKD NOD (B). CKD 5D: dialysis-requiring chronic kidney disease stage V; CKD NOD: chronic kidney disease not requiring dialysis; iPTH: intact parathyroid hormone; BAP: bone specific alkaline phosphatase

Parameter	Mixed uremic osteodystrophy					All high turnover renal osteodystrophy				
	ROC	P value	Cutoff	Sens.	Spec.	ROC	P value	Cutoff	Sens.	Spec.
A) CKD 5D										
iPTH (pmol/l)	0.90	<0.001	14.5	0.93	0.93	0.83	0.003	12.8	0.83	0.91
BAP (U/l)	0.48	0.844	17.5	0.60	0.57	0.37	0.252	17.5	0.50	0.46
B) CKD NOD										
iPTH (pmol/l)	0.89	0.089	13.7	1.00	0.85	0.91	0.019	13.5	1.00	0.91
BAP (U/l)	0.96	0.042	23.9	1.00	0.92	0.93	0.013	19.8	1.00	0.91

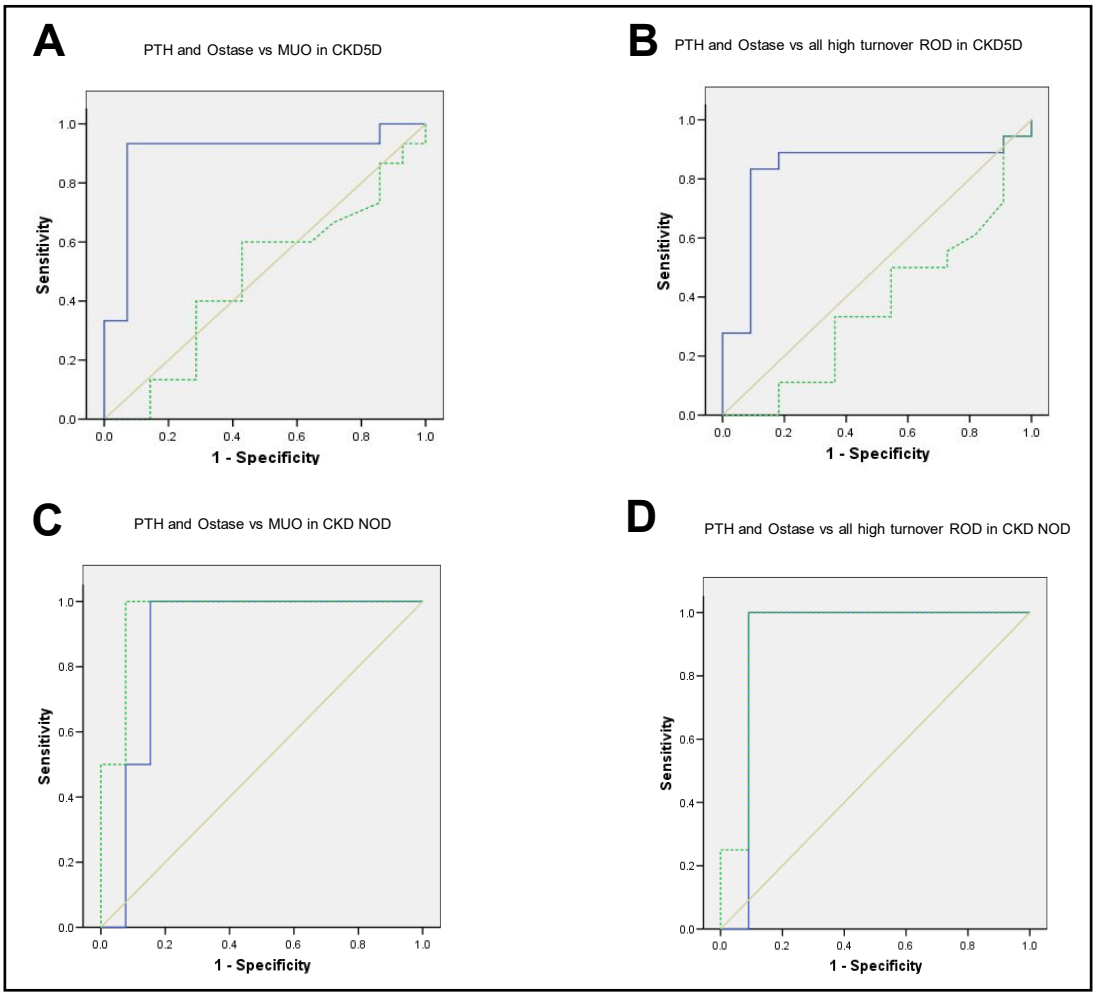

Fig. 1. A) Receiver operator characteristic (ROC) curve of iPTH (solid line, ROC 0.90, cutoff 14.5 pmol/l) and bone-specific alkaline phosphatase (BAP, dotted line, ROC 0.48, cutoff 17.5 U/l). Association with high turnover uremic osteodystrophy. Analysis based on dialysis-requiring CKD 5D with mixed uremic osteodystrophy (MUO or Delling class III) as the outcome variable. B) Receiver operator characteristic (ROC) curve of iPTH (solid line, ROC 0.83, cutoff 12.8 pmol/l) and bone-specific alkaline phosphatase (BAP, dotted line, ROC 0.37, cutoff 17.5 U/l). Association with high turnover uremic osteodystrophy. Analysis based on dialysis-requiring CKD 5D with all types of high-turnover renal osteodystrophy (ostitis fibrosa and mixed uremic osteodystrophy or Delling class I and III) as the outcome variable. C) Receiver operator characteristic (ROC) curve of iPTH (solid line, ROC 0.89, cutoff 13.7 pmol/l) and bone-specific alkaline phosphatase (BAP, dotted line, ROC 0.96, cutoff 23.9 U/l). Association with high turnover uremic osteodystrophy. Analysis based on CKD NOD with mixed uremic osteodystrophy (MUO or Delling class III) as the outcome variable. D) Receiver operator characteristic (ROC) curve of iPTH (solid line, ROC 0.91, cutoff 13.5 pmol/l) and bone-specific alkaline phosphatase (BAP, dotted line, ROC 0.93, cutoff 19.8 U/l). Association with high turnover uremic osteodystrophy. Analysis based on CKD NOD with all types of high-turnover renal osteodystrophy (ostitis fibrosa and mixed uremic osteodystrophy or Delling class I and III) as the outcome variable.

Discussion

In this retrospective analysis of bone biopsy results and their association with blood biomarkers of bone turnover, the main finding was a strong association of iPTH with high bone turnover renal osteodystrophy in patients with CKD NOD as well as patients with CKD

5D. In the former patient group, elevated BAP and to some degree perhaps acidosis also appeared to be associated with high turnover renal osteodystrophy. Unexpectedly and in contrast to most other published investigations of this kind, the iPTH threshold, above which high turnover renal osteodystrophy becomes likely to be found on biopsy, was significantly lower than previously reported in studies based on CKD 5D populations [8-10].

For example, the study by Barreto et al. [9] identified a threshold of 300 pg/ml (31.8 pmol/l) for the detection of high turnover renal osteodystrophy, which is more than 2 times higher than ours. On the other hand, that study was performed in a different patient population, in which for example the prevalence of aluminum intoxication was much higher than in our patient population, where this condition is generally rare. But beyond this discrepancy in the threshold of iPTH for the detection of high turnover renal osteodystrophy, in comparison with the study by Barreto et al., our results also support the notion that iPTH might be used to detect high turnover renal osteodystrophy in CKD 5D patients, perhaps also obviating the need to perform a bone biopsy. This observation stands in contrast to other previously published work. For example, Gal-Moscovici and Popovtzer could not find an association of iPTH level with bone turnover [8]. Interestingly, in their study, the prevalence of low-turnover bone disease was much higher compared to our results and the most prevalent subtype of high turnover renal osteodystrophy found in that study was ostitis fibrosa as opposed to mixed uremic osteodystrophy in our study. These significant differences may play an important role explaining the substantially discrepant results.

The now three decades old study of von Herrath et al. [6] like ours, has also been performed in Germany, used the Delling's histological criteria and interestingly, like our study, neither did it employ tetracycline labelling nor histomorphometric analyses. Therefore, it had many similarities with our investigation. On the other hand, aluminum intoxication, like in the study by Barreto et al., was very prevalent in this older report by von Herrath et al. due to the widespread use of aluminum-based phosphate binders or water contamination during that therapeutic era [6]. Nonetheless and again, elevated iPTH was found to be associated with high turnover renal osteodystrophy, but required much higher levels of iPTH, in excess of 300 pmol/l (2829 pg/ml), even if compared to the results of Barreto et al. [9] and our study.

If the results of our study were reproducible in a wider population and/or in different geographic regions, it might indicate that the current iPTH thresholds to trigger therapeutic interventions for the suppression of bone turnover need to be reconsidered and should be lower than currently estimated. In this context, a comparison of our results with the much larger and more recent study by Sprague et al. [10], is of interest. That study included bone biopsy results of 492 CKD 5D patients from the four countries Brazil, Portugal, Turkey and Venezuela. iPTH levels of 103.8 pg/ml (11.0 pmol/l) and 323.0 pg/ml (34.3 pmol/l) were found to discriminate between low and non-low as well as high and non-high turnover bone disease, respectively. Our cutoff level (12.8 pmol/l (120.7 pg/ml) for CKD 5D and 13.5 pmol/l (136.7 pg/ml) for CKD NOD) finds itself at the lower end of this spectrum. One could speculate that the difference in results might stem from differences in the patient population, since in the study by Sprague et al., the prevalence of high turnover bone disease was much smaller with 17% compared with our study (30% in CKD NOD and 66% in CKD 5D). In addition, there were likely substantial differences in treatment, with ca. 77% of participants receiving calcium and 10% aluminum-containing phosphate binders. By comparison, our study population takes non-calcium containing binders much more and calcium less frequently and does not use aluminum.

Another difference of the present study in comparison with previous work is the inclusion of patients with CKD NOD. Although this group is small with only 33 subjects, an interesting observation can be made. The estimated iPTH cutoff levels above which the diagnosis of high-turnover osteodystrophy becomes likely (13.5 pmol/L [127.3 pg/ml]) do not differ substantially from those observed in CKD 5D patients (12.8 pmol/L [120.7 pg/ml]). This stands in contrast to both the K-DOQI [14, 15] and KDIGO [16] recommendations, which suggest a differentiated response to elevated iPTH in patients with CKD NOD and CKD 5D.

Treatment in CKD NOD patients is recommended if iPTH rises above the upper normal limit while emphasizing that the optimum level in this group is not known. In contrast, for CKD 5D patients it is recommended that the iPTH level ranges 2-9 times above the upper normal limit [14-16]. Therefore, a more permissive approach to increases in iPTH is suggested for patients with CKD 5D than can be supported by the results of the present study. The latter suggests similarly low thresholds for iPTH above which high-turnover osteodystrophy can be found. Both guidelines emphasize, however, that it is not the goal to control isolated laboratory values but manage organ damage caused by metabolic derangements in CKD-MBD.

Certainly, our study has significant weaknesses, which might limit its validity and applicability in other patient populations. For instance, it is retrospective in nature with several data points missing as is often the case in such a design, which can further only identify statistical associations and does not confirm causation. It is a single center study from a homogenous central European, mostly Caucasian population, which limits its validity for other geographic and ethnic patient populations. In addition, this retrospective study is based on samples obtained within the context of routine clinical work, making its results subject to bias by indication. The sample size is also small which may introduce further bias. Finally, and importantly, tetracycline labeling would have enhanced the sensitivity of the bone turnover estimation in the investigated samples and would have allowed for a quantitation of mineralization status, mineral apposition rate, bone turnover and rate of bone formation [5]. On the other hand and notwithstanding the recent, much larger study by Sprague et al., only few similar studies have been performed previously. Moreover, previous work in this area is characterized by conflicting results and, like in our study, similarly small sample sizes and other problems such as high prevalence of aluminum intoxication. Therefore, and ideally, future multinational, multicenter studies and better, prospectively collected registries of bone biopsies and accompanying laboratory findings need to be performed in order to obtain more definitive results that might ultimately affect treatment recommendations.

Conclusion

In a single center, retrospective analysis, iPTH level was positively associated with the histological finding of high turnover renal osteodystrophy on bone biopsy in patients with CKD. In addition, BAP was positively and pH negatively associated with the same finding, but only in the subgroup of patients with CKD NOD. A plasma iPTH level of approximately 12-14 pmol/l (approx. 113-132 pg/ml) provided a sensitive and specific threshold for the detection of high turnover renal osteodystrophy on bone biopsy among patients with CKD in this analysis and thus appears to be lower than supported by the current management guidelines. More research is needed, particularly in larger and more diverse patient populations to confirm these findings.

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Disclosure Statement

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