

Bone markers in renal osteodystrophy

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Chronic kidney disease-mineral and bone disorders

✓ Along with the progression of chronic kidney disease (CKD), the kidney gradually became insufficient to maintain systemic homeostasis, resulting in various abnormalities of bone and mineral metabolism.

Type	Laboratory abnormalities	Bone disease	Calcification of vascular or others soft tissue
L	+	-	-
LB	+	+	-
LC	+	-	+
LBC	+	+	+

Mee et al. Kidney International 2005

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Renal osteodystrophy (ROD)



The term ROD is specific to bone pathology found in patients with CKD

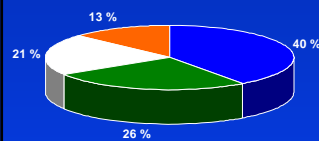
Bone biopsy is required for the evaluation and diagnosis of ROD

Turnover	Mineralization	Volume
Low	Normal	Low
Normal	Normal	Normal
High	Anormal	High

Mee et al. Kidney International 2005

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Prevalence of different forms of ROD



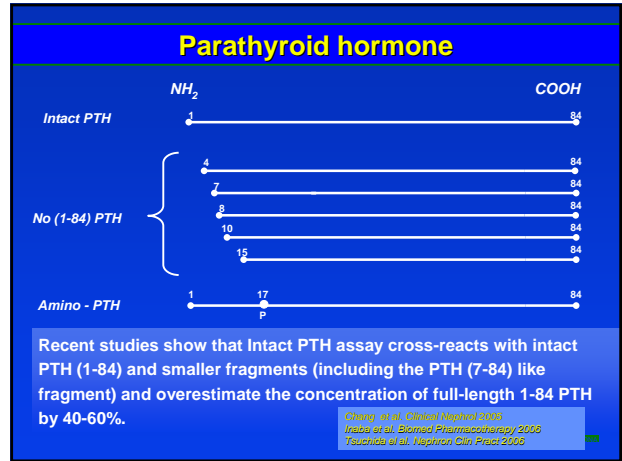
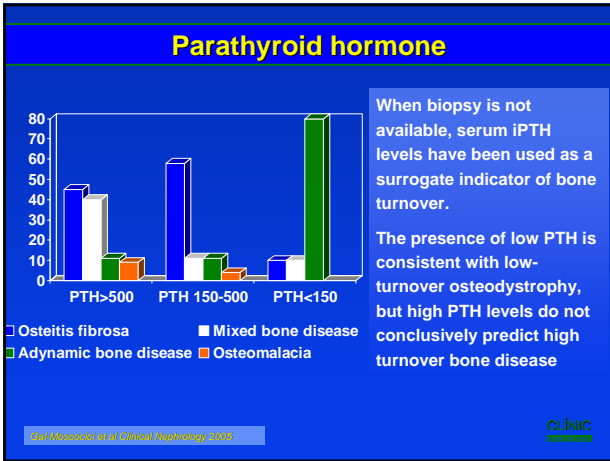
40% of patients showed high bone turnover disease compatible with osteitis fibrosa cystica

60% present low- or normal bone turnover disease

- High bone turnover (Osteitis fibrosa cystica)
- adynamic bone disease
- mixed bone disease
- osteomalacia

Geis-Monod et al. Clinical Nephrology 2005

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iPTH limitations in ROD

- What is the most useful in the diagnosis of ROD?
 - Second-generation assay detects PTH 1-84 and non iPTH fragments
 - Third-generation assay detects PTH 1-84
- What are reflecting iPTH levels?
 - Degree of parathyroid gland activity
 - Bone turnover
- Resistance of bone cells to PTH action.
 - Relationship between serum iPTH and BFR is not always maintained

Cheng et al. Clinical Nephrol 2005
 Inaba et al. Clinical Pharmacotherapy 2000
 Tsuchida et al. Nephron Clin Pract 2002

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Bone markers in ROD

	Renal excretion
Total ALP	No
Bone ALP	No
PINP	No
PICP	No
OC	Yes
TRACP	No
PYR	Yes
D-PYR	Yes
CTX	Yes
NTX	Yes

Serum markers of bone remodeling can be useful to evaluate ROD. Most bone makers have renal metabolism and/or excretion and accumulate in renal failure. Urinary bone markers values may change due to the reduction of creatinine excretion.

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Bone markers in ROD

	Renal excretion	
	No	N-fold high
Bone ALP	No	Normal
PINP	No	1.3
OC	Yes	6.5
PYR	Yes	18.4
D-PYR	Yes	5.1
CTX	Yes	4.4
NTX	Yes	6.2

Bone markers with renal metabolism increased in renal failure.

In some cases, a correlation persists between these markers and histomorphometric parameters or BMD evolution.

Masano et al. Clinical Chemistry 2003

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Bone markers in ROD

	High turnover	Normal/Low turnover	P
iPTH	831±707	142±150	0.007
Total ALP	282±224	171±78	NS
Bone ALP	70±64	11±4.4	0.009
OC	555±423	198±261	0.02
PICP	254±118	200±33	NS
ICTP	33±17	40±5.9	NS
Free PYR	109±108	34±13	0.04

Patients with high bone turnover disease exhibit significantly higher values of bone ALP, OC, and PYR than patients with normal or low turnover disease.

These markers have a satisfactory correlation with histomorphometric parameters of bone turnover.

Bone ALP emerged as one of the most sensitive markers.

Ueda et al. J Clin Invest 1999

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Bone markers in low bone turnover osteodystrophy

Low turnover	iPTH	total ALP	Bone ALP	OC	TRACP	D-PYR
Cut off values	79.7	82.5	13	36.2	5.98	21.5
Sensitivity %	88.8	75	100	87.5	80	88.89
Specificity %	93.7	100	93.8	86.7	96.1	93.75
Youden's index*	0.82	0.75	0.93	0.74	0.76	0.82

* Youden's index (determine the optimal discrimination limit for each test) = sensitivity+specificity-1

The analysis of the discriminant power of each marker in identifying low turnover disease showed that the highest levels of Youden's index were provided by bone ALP, while D-PYR was at the same levels as intact PTH.

Coan et al. Nephrol Dial Transplant 1998

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Bone markers high bone turnover disease

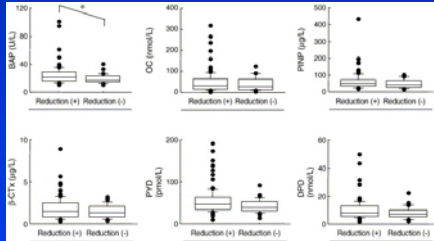
High turnover	iPTH	total ALP	Bone ALP	iPTH _{≥200+} bone ALP _{≥20}
	≥200	≥200	≥20	
Sensitivity %	72	50	100	100
Specificity %	80	90	100	80
PPV %	92	94	84	94
NPV %	47	36	100	100

Bone ALP equal or higher than 20, alone or combined with intact PTH of 200, had the highest sensitivity, specificity, and predictability values for the diagnosis of high-turnover disease, and excluded patients with normal or low turnover disease.

Ueda et al. J Am Soc Nephrol 1996

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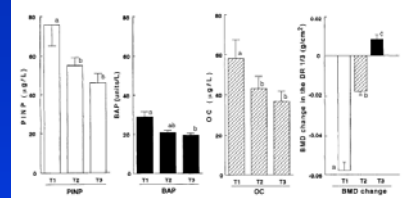
Serum bone ALP and bone loss



Hemodialysis patients with higher levels of bone ALP showed a BMD reduction, suggesting that bone ALP could also be useful to discriminate between patients with and without bone mineral density loss.

Ueda et al. Life Sciences 2005

Serum PINP in hemodialysis patients



PINP and OC levels were different between group, being higher in patients who lost BMD and lower in those with decreasing tertiles of bone loss.

PINP correlated with bone changes and bone formation and resorption markers.

PINP has a very strong correlation with bone ALP, that explain 91% of the variability of bone ALP.

Yoshida et al. J Renal Disord
Cavaliari et al. Clinics Chimica Acta 2006

Serum osteocalcin

There is a good correlation of OC with bone histomorphometric parameters in hemodialysis patients

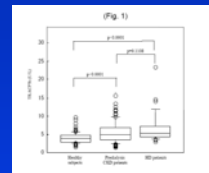
In predialysis patients OC levels have been found to be a valuable marker for the diagnosis of adynamic bone disease.

	Sensitivity %	Specificity %	Youden's Index
Bone ALP \leq 23	72	66	0.49
OC \leq 41	83	67	0.50
iPTH \leq 237	78	53	0.31

*P<0.001

Clinical Endocrinology Postprint

Tartrate-resistant (type 5b) acid phosphatase



Serum TRACP5b levels are higher in CKD patients.

Multiple regression analysis showed that iPTH was independently associated with TRACP5b. Moreover, no association between GFR and TRACP5b was detected.

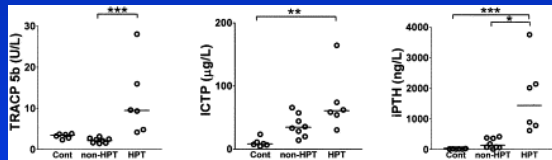
Log (TRACP5b)	
GFR	-0.159
Log iPTH	0.397*

*P<0.001

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Clinical Endocrinology Postprint

Tartrate-resistant (type 5b) acid phosphatase



Serum TRACP5b levels were higher in patients with high bone-turnover disease.

Chou et al. Am J Kidney Dis. 2003

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Tartrate-resistant (type 5b) acid phosphatase

TRACP levels had a better correlation with histomorphometric parameters of bone resorption than iPTH, and strongly correlated with histological parameters of osteoclast activity.

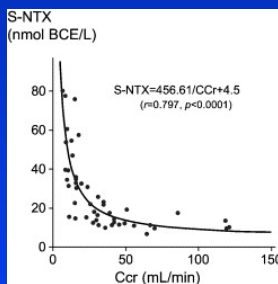
	iPTH	TRACP5b
OC surface/bone surface	0.762*	0.916*
N° Osteoclast	0.815*	0.908*
BFR/BS	0.677 **	0.906*
MAR	0.866*	0.9*
Erosion depth	0.782*	0.66**
Erosion surface/bone surface	0.588 **	0.501 **

*P<0.001; ** P<0.05

Chou et al. Am J Kidney Dis. 2003

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Serum NTX in predialysis patients



Bone resorption markers derived from collagen type I degradation increases as renal function declines.

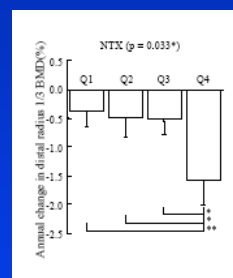
Serum NTX showed a very strong inverse hyperbolic correlation with creatinine clearance

*P<0.001

Strom et al. Bone et al. 2005

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Serum NTX and bone loss



Serum NTX showed a significant correlation with intact PTH and bone resorption and formation markers

Patients with increased concentration of NTX had a faster rate of bone loss.

Mason et al. Clinical Chem 2005

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Serum NTX and bone loss

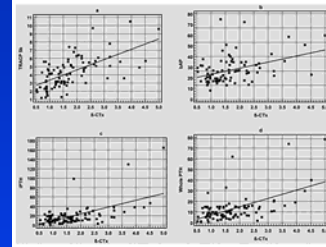
	Sensitivity %	Specificity %	Youden's Index	PPV %	NPV %
iPTH	31	75	0.03	28	75
Bone ALP	38	80	0.18	39	79
sNTX	48	83	0.31	50	82

Values of NTX in the highest quartile had a very good predictive capacity to identify patients with bone mineral density loss, the sensitivity, specificity and positive and negative predictive values being similar to those of intact PTH

Marrero et al. *Clinical Chem* 2003

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Serum CTX



There is a highly significant correlation between CTX and intact and whole PTH, and between CTX and biochemical markers of bone resorption and formation.

Reichrath et al. *Nephron Clin Pract* 2004

Serum CTX and bone loss

	Sensitivity %	Specificity %	Youden's Index	ppv %	NPV %
iPTH	26	86	0.12	48	69
Bone ALP	43	84	0.27	58	74
βCTX	41	83	0.24	55	73

Moreover, increased levels of CTX were associated with a faster rate of bone loss.

In this study CTX had a similar predictive value than the other remodeling markers, and was not inferior to intact PTH.

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Olivero et al. *Osteoporos Int* 2003

Bone resorption markers and bone loss

	OR (95%CI)	P
iPTH	1.48 (1.03-2.1)	0.033
βCTX	1.73 (1.24-2.4)	0.001
PYR	1.52 (1.11-2.08)	0.009
D-PYR	1.64 (1.18-2.27)	0.003
Bone ALP	1.69 (1.23-2.32)	0.001

There was a significant increase in risk of bone loss associated with the increase of CTX, similar to the other markers.

The increased in PYR and D-PYR was also associated with an increased in the risk of bone loss.

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Olivero et al. *Osteoporos Int* 2003

SUMMARY

- Bone alkaline phosphatase can be considered as the more useful bone marker in the diagnosis of renal osteodystrophy, improving the predictive value of intact PTH.
- Among bone resorption markers, TRACP5b emerges as a promising marker, unaffected by renal function and with good correlation with histomorphometric data.
- The usefulness of PINP must be more intensively investigated in studies that include bone biopsy.

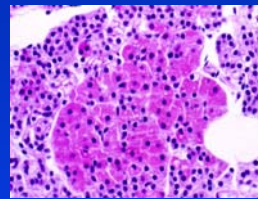
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PRACTICE

SUMMARY

- Osteocalcin and bone resorption markers derived from collagen type I degradation had renal metabolism and/or excretion and accumulate in renal failure. In spite of their correlation with histomorphometric parameters or bone loss, they should not be considered among the first options in the evaluation and diagnosis of renal osteodystrophy

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PRACTICE

Parathyroid hormone



Synthetic PTH(7-84) have different or antagonistic biological activity than PTH (1-84).

PTH(7-84) decreased the hypercalcemic and phosphaturic effects of 1-84 PTH and possibly play a role in the skeletal resistance to PTH.

Renal dysfunction causes accumulation of PTH(7-84) in serum by impairing its urinary excretion.

New assays has been developed in order to measure exclusively the 1-84 PTH, but their predictive value in ROD need further evaluations.

Cheng, et al. Clinical Nephrol 2005
Dobin et al. Clinical Pharmacology 2008
Fauci et al. Nephron Clin Pract 2009

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