

Alkaline phosphatase bone isoform B1x - a marker of impaired osteoblastic function in patients with renal osteodystrophy

Mathias Haarhaus^{a,b}, Marie-Claude Monier-Faugere^c, Per Magnusson^{a*}, Hartmut H. Malluche^{c*}

^a Division of Clinical Chemistry, Department of Clinical and Experimental Medicine, Faculty of Health Sciences, Linköping University, Linköping, Sweden

^b Department of Nephrology, Karolinska University Hospital, Stockholm, Sweden

^c Division of Nephrology, Bone and Mineral Metabolism, University of Kentucky, Albert B. Chandler Medical Center, Lexington, USA

* These authors contributed equally as senior authors.



Linköping University
FACULTY OF HEALTH SCIENCES

Introduction

Renal osteodystrophy encompasses the bone histologic abnormalities seen in patients with chronic kidney disease (CKD). The bone-specific alkaline phosphatase (BALP) isoform B1x is exclusively found in serum of some CKD patients. The aim of this study was to examine the relationship between serum BALP isoform activities and histomorphometric parameters of bone in patients with CKD on chronic dialysis.

Methods

Anterior iliac crest bone biopsy samples from 40 CKD patients were selected on the basis of bone turnover for histomorphometric analysis. There were samples from 20 patients with low and 20 with non-low bone turnover. In serum, BALP, BALP isoforms (B/I, B1x, B1 and B2), and parathyroid hormone (PTH) were measured.

Bone histomorphometric parameters in patients on hemodialysis with absence or presence of the circulating BALP isoform B1x

	B1x absent (n = 19)	B1x present (n = 21)
Parameters of bone structure		
Bone volume/Tissue volume (%)	20.1 (16.5-23.1)	19.8 (15.8-24.7)
Trabecular thickness (µm)	109 (74.7-120)	93.9 (79.7-110)
Trabecular separation (µm)	342 (295-546)	375 (305-475)
Static parameters of bone formation		
Osteoid volume/Bone volume (%)	8.25 (5.20-20.8)	6.44 (3.95-13.0)
Osteoid surface/Bone surface (%)	43.8 (24.6-54.6)	35.2 (15.7-46.5)
Osteoid thickness (µm)	13.1 (9.79-15.1)	10.2 (8.28-14.6)
Number of osteoblast/bone perimeter (#/100 mm)	178 (61.5-349)	33.5 (10.5-136) [#]
Parameters of bone resorption		
Erosion surface/Bone surface (%)	2.44 (1.56-6.15)	0.98 (0.55-3.01)
Erosion depth (µm)	13.0 (11.8-16.4)	11.0 (9.04 -13.8)
Number of osteoclast/Bone perimeter (#/100 mm)	23.8 (14.3-80.7)	12.9 (10.8-30.7)
Dynamic parameters		
Mineral apposition rate (µm/d)	0.83 (0.75-0.93)	0.52 (0.10-0.88) [*]
Mineralizing surface/Bone surface (%)	6.52 (4.32-12.6)	3.17 (0.80-8.7) [*]
Bone formation rate/Bone surface (mm ³ /cm ² /yr)	2.43 (1.57-3.86)	0.55 (0.03-3.04) [*]
Activation frequency (yr ⁻¹)	0.57 (0.33-0.65)	0.16 (0.01-0.65) [*]
Mineralization lag time (days)	70.1 (46.1-136)	225 (90.1-972) [#]
Bone formation rate/osteoblast (mm ³ /cell/yr*10 ³)	15.3 (5.07-38.5)	9.97 (2.59-21.6)
Osteoblast vigor (%/day)	0.49 (0.23-0.62)	0.14 (0.02-0.37) [*]

Data are expressed as median (lower quartile to higher quartile).

^{*}p < 0.05; [#]p < 0.01

Conflict of interest statement

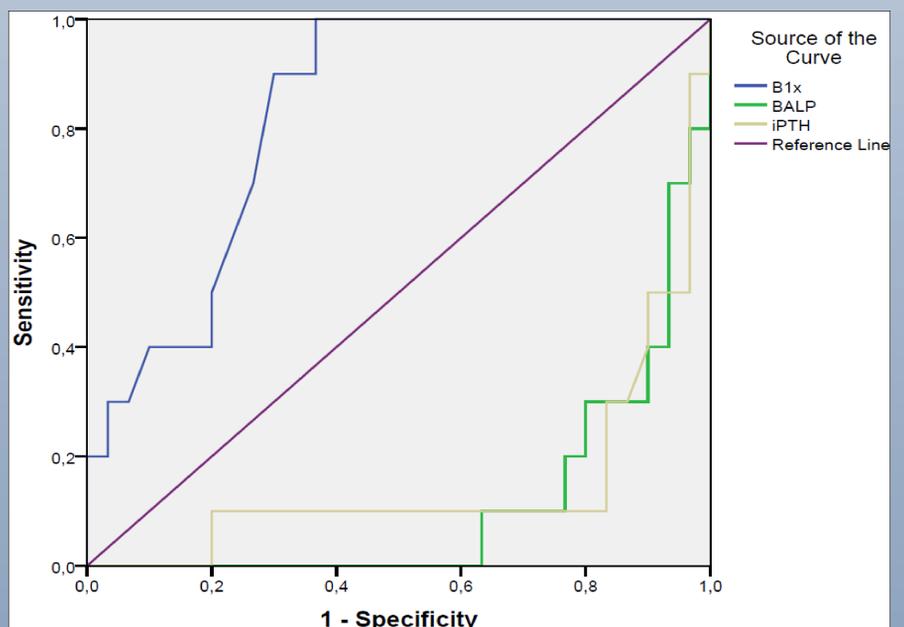
The authors have no conflict of interest to disclose.

Results

B1x was found in 21 patients (53%). They had lower levels of BALP, other BALP isoforms, and PTH compared to patients without B1x. B1x correlated inversely with osteoblast number and activity. ROC curves showed that B1x was superior to PTH and BALP to diagnose low osteoblast activity.

Conclusion

The study shows that B1x is a novel diagnostic parameter for osteoblastic insufficiency as illustrated by superior ROC curve AUC compared to PTH and BALP. This indicates that the release of B1x into serum from bone is a sign of perturbed osteoblast activity.



Receiver operator characteristic (ROC) curve for diagnosis of low mineral apposition rate (MAR)

AUC: B1x 0.828 (p < 0.01), BALP 0.113 (p < 0.001), and PTH 0.148 (p = 0.001).

Correlation coefficients of markers of bone metabolism and histomorphometric parameters

	N.Ob/B.Pm	Ob.Vg	BFR/BS	MAR	Mlt	MS/BS
B/I	0.18	0.12	0.08	0.03	-0.10	0.09
B1x	-0.30 [*]	-0.26 [*]	-0.26 [*]	-0.29 [*]	0.28 [*]	-0.25 [*]
B1	0.19	0.16	0.16	0.14	-0.15	0.17
B2	0.28 [*]	0.19	0.20	0.16	-0.18	0.20
BALP	0.43 ^{***}	0.38 ^{**}	0.39 ^{**}	0.36 ^{**}	-0.37 ^{**}	0.38 ^{**}
PTH	0.40 ^{***}	0.39 ^{**}	0.37 ^{**}	0.33 ^{**}	-0.35 ^{**}	0.37 ^{**}

BALP, bone specific alkaline phosphatase; B/I, B1x, B1, B2, isoforms of BALP; PTH, parathyroid hormone; N.Ob/B.Pm, number of osteoblast per bone perimeter; Ob.Vg; osteoblast vigor; BFR/BS, bone formation rate per bone surface; MAR, mineral apposition rate; MS/BS, mineralizing surface per bone surface; BFR/Ob, bone formation rate per osteoblast; Mlt, mineralization lag time. ^{*} = P<0.05, ^{**} = P<0.01, ^{***} = P<0.001