Clinical significance of bone alkaline phosphatase isoforms, including the novel B1x isoform, in mild to moderate chronic kidney disease

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Abstract

Background. Mineral bone disorder (MBD) is a common complication of chronic kidney disease (CKD) even during the early stages. Bone alkaline phosphatase (BALP) is a marker of bone formation and plays a pivotal role in the mineralization process. Three BALP isoforms (B/I, B1 and B2) have been identified in healthy individuals and a fourth isoform (B1x) has been discovered in serum from dialysis patients. We investigated these BALP isoforms, type I procollagen intact amino-terminal propeptide (PINP), carboxy-terminal telopeptide of type I collagen (CTX) and tartrate-resistant acid phosphatase isoform 5b (TRACP5b), as well as bone mineral density (BMD) in predialysis CKD patients.

Methods. PINP, CTX, TRACP5b and BALP isoforms were analysed in serum from 46 patients within CKD stages 3–5. BMD was determined by dual-energy x-ray absorptiometry.

Results. PINP, TRACP5b and the BALP isoforms, B/I, B1 and B2, were independent predictors of total hip BMD in all patients. Furthermore, B/I predicted osteopaenia in the hip and in the distal 1/3 of the radius in CKD stage 3. The B1x isoform was detected in nine patients (20%), who had lower GFR, higher phosphate and calcium × phosphate product.

Conclusion. We found an association of BALP isoforms and other markers of bone turnover with total hip BMD, which predominantly comprises trabecular bone. The association of the new BALP isoform B1x with risk factors for vascular calcification leads us to hypothesize a possible role for B1x in this process. The significance of the BALP isoforms in CKD remains to be further explored in experimental and clinical settings in conjunction with bone histomorphometry.

Keywords: alkaline phosphatase; bone mineral density; bone turnover; mineral bone disorder; predialysis

Introduction

Mineral and bone disorders (MBD) are common findings in patients with chronic kidney disease (CKD). The spectrum of CKD–MBD ranges from high-bone turnover osteitis fibrosa to low-bone turnover diseases such as osteomalacia and adynamic bone disease [1]. Histomorphometric studies have demonstrated all forms of renal osteodystrophy in early stages of CKD [2,3]. Both low- and high-bone turnover diseases in patients on haemodialysis are associated with increased skeletal as well as cardiovascular morbidity and mortality [4–6]. It is, therefore, of great importance to prevent and treat bone and mineral metabolic abnormalities. It has also been reported that CKD patients are at risk of developing adynamic bone disease during treatment of secondary hyperparathyroidism [7]. Reliable diagnostic tools for the assessment of bone turnover are therefore necessary for an accurate treatment of CKD–MBD.

An iliac crest biopsy with bone histomorphometry is the ‘gold’ standard for the classification of renal bone disease [8]; however, this is seldom applied in clinical care. Less invasive diagnostic approaches, such as biochemical markers of bone turnover, are of potential value as diagnostic indicators of renal bone disease [9]. These markers can be divided into markers of bone resorption, such as the type I collagen carboxy-terminal telopeptide (CTX) and tartrate-resistant acid phosphatase isoform 5b (TRACP5b), and markers of bone formation, such as bone-specific alkaline phosphatase (BALP) and type I procollagen intact amino-terminal propeptide (PINP). The relationship between bone pathology and biochemical markers of bone turnover in dialysis patients, as well as in patients during the earlier CKD stages, has been studied to some extent [10–15]. Nevertheless, no single marker has been established to accurately distinguish between the different types of renal bone disease [16].

Alkaline phosphatase (ALP) is a glycoprotein and functions as an ectoenzyme attached to the outer surface of...
Bone ALP isoforms and BMD in CKD patients

osteoblasts and matrix vesicles. Studies of the inborn error of metabolism, hypophosphatasia, caused by missense mutations of the tissue-nonspecific ALP gene have provided compelling evidence for an important role for BALP during the development and mineralization of the human skeleton [17,18]. At least six different ALP isoforms can be separated and quantified by weak anion-exchange high-performance liquid chromatography (HPLC) in serum from healthy individuals: one bone/intestinal (B/I), two bone (B1 and B2) and three liver ALP isoforms (L1, L2 and L3) [19]. The circulating levels of these three BALP isoforms can vary independently during the pubertal growth spurt [20] and in several disease states such as growth hormone deficiency [21]. X-linked hypophosphataemia [19] and metastatic bone disease [22]. These isoforms differ also in their distribution in different skeletal sites with respect to cortical and trabecular bones [23]. Previously, we have demonstrated the presence of a new BALP isoform, B1x, in serum from dialysis patients, which was not detected in serum from healthy individuals [24,25].

Low bone mineral density (BMD) is associated with skeletal and vascular complications in individuals with normal renal function and in dialysis patients [26–28], and BMD decreases as the glomerular filtration rate (GFR) decreases in predialysis CKD [15]. Biochemical markers of bone turnover and BMD have been examined in both predialysis and dialysis patients, however, with varying results [13,15,29,30]. In a recent publication, Moe et al. [16] emphasized the need for intensified research to clarify the role of biochemical markers of bone turnover and their association with BMD in CKD patients. In particular, they called for research on the more specific markers of bone turnover such as PINP, TRACP5b and CTX, in CKD stages 3–5.

This study was designed to investigate the significance of the BALP isoforms for the prediction of BMD in patients with predialysis CKD. Furthermore, we also examined the relationship between the BALP isoforms and PINP as markers of bone formation as well as CTX and TRACP5b as markers of bone resorption in relation to BMD.

Subjects and methods

Patients and control subjects

Patients were recruited from the nephrology outpatient clinic at Linköping University Hospital between 2003 and 2005, and inclusion was conducted during the winter semiannum to avoid a potential influence of the seasonal variation from vitamin D and parathyroid hormone (PTH). All patients with a calculated creatinine clearance of ≤60 mL/min/1.73 m² during ≥12 months were screened for inclusion. Exclusion criteria were chronic treatment with systemic corticosteroids or lithium, and mental retardation. Forty-six patients, 15 females and 31 males, age 28–86 years, were included after informed consent. GFR ranged from 11 to 59 mL/min/1.73 m². The patients were categorized into groups in accordance with the KDOQI classification [31]: CKD stage 3 (n = 23), stage 4 (n = 15) and stage 5 (n = 8). Underlying nephropathy types were nephrosclerosis (n = 13), diabetic nephropathy (n = 12), chronic glomerulonephritis (n = 11), chronic tubulo-interstitial nephritis (n = 5), polycystic kidney disease (n = 1) and unknown (n = 4). Thirty-eight percent of the patients were treated with alfacalcidol. The patients were compared with a control group comprising 153 healthy individuals age 21–90 years (108 females and 45 males). The local research ethics committee of Linköping University, Sweden, approved this study.

Biochemical determinations

GFR was determined by single-sample iohexol clearance (N = 42) or creatinine clearance calculated from a 24-h urine sample (N = 4). Blood and 24-h urine samples were obtained at the time of measurement of iohexol clearance. The serum samples were stored at −70°C prior to analysis.

Serum intact PTH was determined by a two-site immunoradiometric assay (Nichols Institute, San Clemente, CA, USA), with a reported reference interval of 12–65 ng/L for healthy adults [32]. Bio-intact PTH, i.e. the biologically active whole PTH molecule 1–84, was measured with an automated immunochemiluminometric assay using a Nichols Advantage analyser (Nichols Institute) as described elsewhere [33]. The reference interval (given by Nichols Institute) by 95% confidence interval for healthy adults (n = 336) is 7–50 ng/L. Serum 25(OH) vitamin D was measured by the Nichols Advantage automated chemiluminescence protein-binding immunoassay (Nichols Institute Diagnostics) [34]. Serum high-sensitivity C-reactive protein (hsCRP) was analysed by an immunoturbidimetric assay on the ADVIA 1650 chemistry system (Siemens Medical Solutions Diagnostics AB, Mölndal, Sweden). It has a particularly wide sensitivity range with the lower limit of detection being 0.12 mg/L [35]. Serum PINP was determined by radioimmunoassay (Orion Diagnostica, Oulunsalo, Finland) [36]. Type I collagen degradation was assessed by the serum CrossLaps enzyme-linked immunosorbant assay (Nordic Bioscience Diagnostics A/S, Herlev, Denmark), which is reported to measure a cathepsin K degradation product of trivalently cross-linked type I collagen, i.e. CTX [37,38]. The serum osteoclast-derived TRACP5b was determined by a solid-phase immunofixed enzyme activity assay (SBA Sciences, Oulu, Finland) [39]. Total ALP was measured by a kinetic assay in a 96-well microtitre plate format [40]. The BALP isoforms B/I, B1x, B1 and B2 were determined by a previously described HPLC method [19,41].

BMD measurements

BMD was measured by dual-energy x-ray absorptiometry using a Lunar Prodigy densitometer (GE Healthcare, Chalfont St. Giles, UK). Measurements were performed in the dominant hip and at the distal 1/3 radius of the dominant arm. Z-scores and T-scores were calculated by comparing with the National Health and Nutrition Examination Survey reference population.

Statistical analysis

Statistics were calculated using SPSS 11.5.1 for Windows (SPSS Inc., Chicago, IL, USA). A critical significance level of 0.05 was chosen. The Mann–Whitney test was used to test differences between two groups, and Kendall’s tau rank correlation coefficient was used for calculation of non-parametric correlations. For the multiple regression analyses, diabetes and gender were treated as dummy variables.

Results

The clinical and biochemical parameters are presented in Table 1. The patients had, on average, 2-fold higher levels of intact and biointact PTH in comparison with the normal reference intervals. Furthermore, CKD patients in stages 4–5 had higher PTH, hsCRP, phosphate and calcium × phosphorus product, in comparison with patients in CKD stage 3, and more patients with diabetes were included in CKD stages 4–5 compared with CKD stage 3. Eighteen patients (39%) were treated with vitamin D. In all cases, the medication consisted of oral alfacalcidol. For two patients, one in CKD stage 3 and one in CKD stage 5, information on vitamin D treatment was missing. The patients on vitamin D treatment had lower GFR (P < 0.01), higher phosphate (P < 0.01), higher calcium × phosphorus product (P < 0.05) and higher iPTH (P < 0.01). We did not detect any significant differences in serum concentrations of any of the examined bone markers, including all BALP isoforms.
in this subgroup of patients treated with vitamin D, and neither were there any differences in BMD at the hip nor at the distal 1/3 radius.

**BALP isoforms and other markers of bone turnover**

The total ALP activity was 3.5 ± 1.3 μkat/L in the group of CKD patients. One patient had a total ALP activity below and 11 patients above the reference interval for healthy adults, 1.6–4.1 μkat/L [24]. The bone ALP isoforms B/I, B1 and B2 were detected in all patients and accounted for 4%, 13%, and 44%, respectively, of the total ALP activity. No significant differences, with respect to the distribution of BALP isoforms, were found between the different CKD stages. Total ALP and all BALP isoforms were significantly higher in CKD stage 3 in comparison with healthy individuals. Only total ALP, B/I and B2 were increased in stage 4 and no significant differences were found in CKD stage 5 (Figure 1). All BALP isoforms correlated with each other, B1 and B2 correlated with TRACP5b and total ALP, B/I, B1 and B2 correlated with PINP. B/I was negatively correlated with total hip BMD. No correlations were found with intact PTH, biointact PTH or 25(OH) vitamin D for the BALP isoforms (Table 2).

**BALP isoform B1x**

The B1x BALP isoform was detected in 9 out of 46 patients (20%). These patients had lower GFR and higher phosphate and calcium × phosphate product. No differences were observed for age, calcium, intact and biointact PTH, 25(OH) vitamin D, other markers of bone metabolism and BMD at all sites (Table 3). B1x was positively correlated with total ALP and all BALP isoforms (Table 2).

**BMD**

The total hip BMD measurements revealed that none of the patients had osteoporosis, but 17 patients had osteopaenia and 27 patients had normal BMD values according to the WHO definition (i.e. osteoporosis, BMD T-score < −2.5 SD; osteopaenia, BMD T-score < −1 SD) [42]. The corresponding patient numbers for the distal 1/3 radius were 4, 6 and 31, respectively. In CKD stage 3, patients with osteopaenia or osteoporosis at the hip as well as at the distal 1/3 radius had higher B/I levels than patients with normal BMD (P < 0.05, respectively). Only intact PTH was higher in patients with CKD stages 4–5 who had osteopaenia or osteoporosis according to their distal 1/3 radius value (P < 0.05). No differences were found in patients with CKD stages 4–5 at the hip.

**Multiple regression analysis of predictors of BMD**

We performed multiple regression analyses using variables with clinical relevance for BMD in an attempt to identify predictors of BMD at total hip and distal 1/3 radius among the examined biochemical markers of bone metabolism. B1x was excluded from these statistical analyses, because it was detected in too few individuals (n = 9). As shown
in Table 4A, total ALP, all three BALP isoforms, PINP and TRACP5b were significant predictors of total hip BMD, whereas none of the bone markers could predict BMD at the distal 1/3 radius (Table 4B).

Discussion

This study demonstrates the presence of the new BALP isoform B1x in predialysis CKD patients. B1x has previously been identified in extracts of human bone tissue [23]. It has also been detected in serum from some (60%) adults on maintenance dialysis treatment and occasionally (7%) in serum from children with CKD [24,25]. B1x has not been observed in healthy individuals or in any other group of investigated patients [19,21,22]. In this study, B1x was detected in 63% of the CKD patients in stage 5, which coincides with our earlier findings in dialysis patients [24]. Our previous observation of an association between low levels of other markers of bone turnover and the presence of B1x could not be confirmed in this study, and neither could we confirm the significant association between B1x and intact PTH. The clinical significance of B1x is, therefore, still unclear. Although B1x was most frequently detected in patients with severe renal failure, it was not found to be correlated with GFR. Neither was its appearance related to vitamin D status or treatment with alphacalcidol. The presence of B1x in serum cannot be explained by accumulation, since none of the ALP isoenzymes and isoforms are cleared from the circulation through the kidneys. Further investigations are warranted, including bone histomorphometry, to better understand the role of B1x in CKD–MBD and renal osteodystrophy.

The associations of B1x in serum with higher serum phosphate and calcium \( \times \) phosphate product, but not with GFR or PTH, lead us to hypothesize that B1x could originate from ectopic tissue calcification. Both high phosphate and calcium \( \times \) phosphate product are associated with vascular calcification [43], whereas the association of PTH with vascular calcification is not as strong [44]. Recent data suggest an association between ALP and vascular calcification, because calcifying vascular smooth muscle cells (VSMC), \textit{in vitro}, increases the expression of ALP [45] and since inhibition of ALP can suppress VSMC...
The circulating ALP activity is correlated with mortality in CKD patients [47]. Future investigations are necessary to elucidate the observed association between B1x and the calcium × phosphate product and, moreover, to study the hypothesized role of B1x in vascular calcification.

The median total ALP activity was significantly higher in healthy controls, which was due to an elevation of all BALP isoforms. As in our previous studies, the difference was most apparent for the B/I isoform. To our knowledge, none of the patients had an active liver disease nor were any other liver enzymes elevated. Neither total ALP nor BALP isoforms were related to vitamin D status or treatment with alphacalcidol. Of note is that only those patients with better-preserved renal function demonstrated a significant increase of the BALP isoform levels in comparison with healthy controls and the BALP isoform B/I was able to distinguish between osteopaenia and normal BMD at the total hip and distal 1/3 radius only within this patient group. With respect to the relatively small number of patients, we did not perform separate multiple regression analyses for the different CKD stages. We conclude that the ability of B/I to differentiate between normal BMD and osteopaenia/osteoporosis in the distal 1/3 radius is lost in more advanced stages of CKD, possibly due to an increase of variation in serum concentrations with decreasing renal function in our patients.

The multiple regression models demonstrated that all the examined markers of bone turnover (with the exception of CTX) predicted total hip BMD, a site predominantly comprising trabecular bone. No significant association was found with BMD at the distal 1/3 radius, which predominantly comprises cortical bone. These compartment-specific differences are consistent with...
previous findings in vivo of a greater abundance of BALP in trabecular bone in comparison with cortical bone [23,48]. The levels of significance for total ALP, PINP and TRACP5b were lower than for isofoms B/I and B1; therefore, we conclude that B/I and B1 are better predictors of total hip BMD than total ALP or the other bone markers examined in this study. Rix et al. [15] reported that BALP was significantly increased in CKD patients in comparison with healthy controls. In the same study, they also found a decline of BMD with decreasing renal function, but the association of BALP with BMD was not further investigated. Lobao et al. [49] described an increased total ALP activity in predialysis CKD with low BMD. In a recent prospective study on patients with predialysis CKD, Obatake et al. [12] found a negative correlation between annual changes of BMD of the distal radius and bone formation markers, which was significant for osteocalcin, but not for BALP. However, the clinical usefulness of osteocalcin in CKD patients is dubious because osteocalcin is cleared by the kidneys [50]. When examining bone density of the distal radius in predialysis patients, Tsuchida et al. [13] demonstrated a stronger correlation of bone turnover markers with trabecular BMD than with cortical BMD, although they did not find an association between trabecular BMD and BALP. Our HPLC method, used in this study for the detection of BALP isofoms, is highly specific [51], whereas the monoclonal antibody against BALP, applied in the assays used by Obatake et al. and Tsuchida et al., has been demonstrated to have some cross-reactivity with liver ALP and, furthermore, does not distinguish the different isofoms of BALP [51].

We found no correlation between total ALP and intact PTH, which is in accordance with our previous study on dialysis patients [24]. Others have described significant correlations between intact PTH and total ALP in CKD stage 5 patients not yet on dialysis treatment [10], as well as in earlier stages of CKD [15]. This incongruence possibly could be explained by the relatively smaller size of our study group and the wide distribution of intact PTH.

The clinical relevance of the BALP isofoms, including the novel BALP isoform B1x, is still hypothetical in the absence of histomorphometric data. Future clinical and experimental investigations, such as determination of vascular calcification and histomorphometric analysis, are necessary to clarify the clinical significance of the BALP isofoms.

In conclusion, we demonstrate, for the first time, the presence of the novel BALP isoform B1x in serum from patients with different stages of CKD not on dialysis treatment, with the most frequent occurrence in patients in CKD stages 4–5. B1x was significantly associated with higher serum

### Table 4. Multiple regression analysis of predictors of BMD: (A) total hip and (B) distal 1/3 radius

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<th>Model 1 Beta</th>
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<td>(B) Distal 1/3 radius</td>
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BMD, bone mineral density; BMI, body mass index; GFR, glomerular filtration rate; PTH, parathyroid hormone; ALP, alkaline phosphatase; B/I, B1x, B1, B2, isofoms of bone alkaline phosphatase; CTX, type I collagen carboxy-terminal telopeptide; TRACP5b, tartrate-resistant acid phosphatase isofom 5b; PINP, type 1 procollagen intact amino-terminal propeptide.

*P < 0.05; **P < 0.01.
phosphate and calcium $\times$ phosphate product, which leads us to hypothesize that B1x could originate from vascular calcification. We have also shown that most of the investigated markers of bone turnover could to some extent predict total hip BMD in patients with moderate CKD.

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Conflict of interest statement. None declared.

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A cut-off value of plasma osteoprotegerin level may predict the presence of coronary artery calcifications in chronic kidney disease patients

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Abstract

Background. Expression of bone proteins resulting from transdifferentiation of vascular smooth muscle cells into osteoblasts suggests that vascular calcifications are a bioactive process. Osteoprotegerin (OPG) could play a key role in bone-vascular calcification imbalance and could be a marker of vascular calcification extent and progression. The purpose of this study was to evaluate relationships between vascular risk biomarkers (including classic risk factors and OPG) and coronary artery calcification (CAC) extent in chronic kidney disease (CKD) patients and to establish within the markers the appropriate cut-off value to predict CAC.

Methods. A total of 133 non-dialyzed CKD patients at various stages of kidney disease [75 males/58 females, median age: 69.9 (27.4–94.6)] were enrolled, excluding extrarenal replacement therapy patients. All underwent chest multidetector computed tomography for CAC scoring. Blood samples were collected for measurement of vascular risk markers (kidney disease, inflammation, nutrition, calcium phosphate and OPG). A potential relationship between CAC and these biological markers was investigated, and a measurement in serum of bone-related degradation products from C-terminal telopeptides of type I collagen. Clin Chem 1998; 44: 2281–2289


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