Bone Alkaline Phosphatase besides Intact Parathyroid Hormone in Hemodialysis Patients – Any Advantage?

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Key Words
Hemodialysis  Bone alkaline phosphatase  Aluminium  iPTH  Renal osteodystrophy

Abstract

Background/Aim: Bone alkaline phosphatase (bAP) is known to be an important biochemical marker of bone formation. Through the present study, we intended to find out whether there is any advantage in bAP determination, as a routine biochemical marker, besides intact parathyroid hormone (iPTH) in hemodialysis patients.

Methods: In a population of 140 hemodialysis patients, bAP and iPTH were determined on four quarterly consecutive occasions. According to the values of iPTH (pg/ml) and bAP (ng/ml), patients were divided into four groups: group I: iPTH >200 and bAP >20, group II: iPTH >200 and bAP <20, group III: iPTH <200 and bAP <20 and group IV: iPTH <200 and bAP >20. Patients with higher serum phosphorus (P) (group A: P ≥ 7 mg/dl) were compared with those with lower serum P levels (group B: P <7 mg/dl). Results: The global correlation between iPTH and bAP (total evaluations, n = 503) was 0.32 (p < 0.001). Group IV patients tended to show a slight increase of serum aluminum (sAl) levels, which were 12.48 ± 5.35 μg/l higher than in the patients from group I (sAl = 9.97 ± 4.39 μg/l), group II (sAl = 10.86 ± 4.45 μg/l) or group III (sAl = 10.92 ± 3.92 μg/l). Significance values (Mann-Whitney) in each group, in comparison with group IV, were the following: group I: 0.004; group II: 0.062; group III: <0.001. Group A (n = 66) showed higher iPTH levels than group B (n = 430), although bAP and sAl were both similar in these two groups of patients (Mann-Whitney): iPTH (A) = 631.0 ± 487.7 vs. iPTH (B) = 253.3 ± 191.6, p < 0.001; bAP (A) = 22.9 ± 17.4 vs. bAP (B) = 20.4 ± 13.1, p = n.s.; sAl (A) = 10.2 ± 3.5 vs. sAl (B) = 10.8 ± 4.4, p = n.s. For similar Al and bAP values, group A showed a much stronger iPTH/bAP correlation than group B: r = 0.67 (p < 0.001) vs. r = 0.30 (p < 0.001), respectively. Conclusion: Although iPTH and bAP are frequently in agreement, it seems important to separate parathyroid activity given by iPTH, from bone remodeling reflected by bAP, in the presence of either a higher aluminum exposition or a well-controlled phosphatemia.
Introduction

Chronic renal failure is often accompanied by alterations in bone metabolism, resulting in an imbalance between bone resorption/formation. Situations in which there is an increase in bone resorption include secondary hyperparathyroidism, osteoporosis, mixed bone diseases and β2-microglobulin osteoarthropathy. On the other hand, lesions in which bone resorption is usually decreased comprehend aluminum-related low bone turnover, osteomalacia, adynamic osteopathy and extraskelatal calcifications [1, 2].

Bone biopsy is the only method that allows a correct diagnosis of the underlying bone disease, through the analysis of both static and dynamic histomorphometric parameters. This method however is not always available since there is a relative lack of experienced technicians and laboratory facilities in this field. On the other hand, it is an invasive method, even though its adverse effects are low [2].

Due to all the reasons mentioned, in the majority of patients, inference of the underlying bone pathology is based on biochemical data, of which the most commonly used is plasma iPTH. However, iPTH has limitations: it primarily reflects the activity of parathyroid glands and not necessarily what goes on in the bone; there may be a relative resistance to its action at the cellular level in chronic renal failure; its measurement through the common laboratorial methods may be overevaluated [1–3].

Bone alkaline phosphatase (bAP) has been considered to be the best biochemical marker of bone formation and it was shown to bring additional information in relation to iPTH [1, 3–5]. bAP is part of a family of six alkaline phosphatase isoenzymes, which have been identified so far (hepatic, intestinal, renal, placental and tumoral). Liver, kidney and bone isofoms are coded by the same gene and differ only by post-transcriptional glycosylation. bAP has a molecular weight of 80 kDa and its plasma concentration depends only on its production, by the osteoblasts, and on its hepatic degradation. It is neither filterable by the kidney, nor dialyzable, and so its plasma concentration is not affected by renal failure [2]. bAP appears to be essential to the mineralization of bone and to its formation [6]. In hemodialyzed patients, values of bAP >20 ng/ml have been associated with either the presence of hyperparathyroidism or with high turnover bone disease [4]. Values of bAP <20 ng/ml associated with iPTH <200 pg/ml (or <3 times the superior limit of the laboratory reference value) suggest the presence of adynamic bone disease (ABD). However, studies that used both bone biopsy results and bAP values in this particular pathology are lacking.

The aim of the present work was to evaluate the usefulness of bAP determination in a population of hemodialyzed patients, by confronting it with iPTH values, in order to get more biochemical information about the underlying bone metabolism.

Patients and Methods

Our sample consisted of a fluctuating population of about 140 chronic renal failure patients undergoing regular hemodialysis, of which 69 were male and 71 were female, with the mean age of 64.12 ± 16.03 years and almost all were Caucasians (10 Black). All patients were dialyzed with polysulfone capillary filters, of either low (conventional hemodialysis) or high permeability (high-flux hemodialysis). Most of the patients were taking calcium carbonate and some were medicated with either oral or intravenous calcitriol at the time of the study. None was medicated with aluminum salts. Also, there were no patients with clinical or laboratorial signs of hepatic disease.

We performed four sequential quarterly predialysis blood samples (total evaluations, n = 503) in order to evaluate plasma iPTH, plasma bAP, serum aluminum (sAl), calsemia and phosphatemia. Plasma iPTH was measured through chemoluminescence by using Immulight 2000® (DPC, USA). Normal values vary between 12 and 72 pg/ml with this method. Plasma bAP was measured by using a monoclonal antibody method (Ostase®). Normal values range from 5.8 to 11.6 ng/ml. sAl was determined by using atomic absorption spectrometry. Plasma calcium and phosphorus were both evaluated through a multichannel autoanalyzer (Hitachi 917®, Roche, Germany).

The statistical analysis was done using the SPSS 9.0 program. Once the distribution was not normal, the Mann-Whitney test was used to compare parameters in different groups. Spearman’s correlation test was used when indicated. Average values are shown and followed by the respective standard deviation in parentheses. Values were considered significant for a p < 0.05, except for linear correlations, where significance was considered for a p < 0.01.

Results

The correlation between bAP and iPTH was 0.32 (p < 0.001) when considering all 503 determinations (fig. 1).

According to the values of both iPTH and bAP, determinations were divided into four groups (table 1). Group I (n = 113) included those analyses in which iPTH was >200 pg/ml and bAP was >20 ng/ml. This concordance of normal or elevated iPTH and high bAP could reflect the presence of either a normal bone or a high remodelling bone disease, or at least it suggests that the presence of ABD would be very unlikely. sAl in this group was quite low, being 9.97 μg/l on average. The correlation
between iPTH and bAP in this group was not significant. Group II (n = 114) comprehended determinations in which iPTH was also >200 pg/ml, but bAP was <20 ng/ml. Average sAl in this group was 10.86 μg/l. Group III (n = 149), including analysis in which both iPTH (<200 pg/ml) and bAP (<20 ng/ml) tended to be low. This could represent the existence of an underlying ABD. sAl in this group was 10.92 μg/l on average. As in groups I and II, the correlation between iPTH and bAP in group III was very low and not significant. Finally, group IV

Table 1. Four groups were created according to the levels of both bAP and iPTH. It is discriminated sAl in each group. Mann-Whitney refers to sAl in each group in comparison with group IV

<table>
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<th></th>
<th>n</th>
<th>sAl (± SD)</th>
<th>p (Mann-Whitney)</th>
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<tbody>
<tr>
<td>GI (iPTH &gt;200 and bAP &gt;20)</td>
<td>113</td>
<td>9.97±4.39</td>
<td>0.004</td>
</tr>
<tr>
<td>GII (iPTH &gt;200 and bAP &lt;20)</td>
<td>114</td>
<td>10.86±4.45</td>
<td>0.062</td>
</tr>
<tr>
<td>GIII (iPTH &lt;200 and bAP &lt;20)</td>
<td>149</td>
<td>10.92±3.92</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GIV (iPTH &lt;200 and bAP &gt;20)</td>
<td>49</td>
<td>12.48±5.35</td>
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Fig. 1. Correlation between bAP and iPTH (a) in the general group, (b) in group A (phosphatemia ≥7 mg/dl), and (c) in group B (phosphatemia <7 mg/dl).
represented those determinations in which iPTH was low (<200 pg/ml) and bAP was high (>20 ng/ml). Interestingly, sAI in this group was higher than in the others, being on average 12.48 μg/l (significance values vs. group I were 0.004, vs. group II were 0.062 and vs. group III were <0.001). The correlation between iPTH and bAP was negative in this group (p = n.s.) (fig. 2).

Determinations were also divided according to serum phosphorus levels. Those with serum phosphorus ≥ 7 mg/dl (group A, n = 66) showed higher iPTH values than those with a phosphatemia <7 mg/dl (group B, n = 430), as expected, although bAP and sAI were both similar in these two groups (table 2). Interestingly, for a similar aluminemia and plasma bAP, those evaluations with a serum phosphorus ≥ 7 mg/dl showed a much stronger iPTH/bAP correlation than the others: r = 0.67 (p<0.001) vs. r = 0.30 (p < 0.001).

**Discussion**

bAP has been shown to be the best marker of bone formation [3, 4]. Several authors have stressed its superiority in relation to iPTH, as we have focused in the introduction above. Indeed there are several works in which both iPTH and bAP were confronted with the histological
results of bone biopsies, either in hemodialysis or peritoneal dialysis patients [1, 3–5, 7]. Unfortunately the method used to measure bAP in these different studies was not the same, making it difficult to draw general conclusions. Anyway, we can expect, with a safe degree of confidence, that values of bAP > 20 ng/ml (Ostase®) in conjunction with values of iPTH > 3 times the superior limit of normal (200 pg/ml in this study) formally excludes a low remodelling bone disease, as it was shown by Ureña et al. [4] in 1996. On the other hand, the presence of low values of bAP (< 7 mg/dl) or iPTH (< 191.6 pg/ml) is highly suggestive of either a normal bone or of a low remodelling bone disease [1, 3, 4, 7]. Even the presence of high values of iPTH by themselves are not sufficient to safely infer the presence of hyperparathyroidism at the bone level, as it was so clearly shown by Goodman et al. [8]. Indeed these authors have demonstrated that some of the dialysis patients, who were submitted to calcitriol therapy in order to control their high remodelling bone disease, developed ABD, in spite of their relatively high levels of iPTH. In this situation, bAP would more realistically reflect the nature of bone metabolism in those patients.

In our study, the correlation between bAP and iPTH in the general group was lower than in other reports. This stresses the relatively high percentage of measures in which iPTH and bAP were not concordant. It is of note, in this regard, that the same happened in those situations in which plasma phosphorus levels were more controlled, and that constituted the vast majority of our measurements. The contrary was also not surprising: those evaluations with higher plasma phosphorus were the ones in which iPTH and bAP showed the best correlation, reflecting the likely stimulation of parathyroid function by phosphorus, giving rise to a likely high remodelling bone disease, as evaluated by the concordance between bAP and iPTH, which tended to be both elevated in this particular population [9].

It was interesting for us to verify that the patients from group IV (higher bAP and lower iPTH) showed higher aluminum levels than the other groups. In this context, it is worthy to remember that Lieberherr et al. [10] have shown that low concentrations of aluminum stimulate the activity of osteoblastic-like cells and in this way, bone formation. On the other hand, the inhibiting effect of aluminum on the parathyroid gland is well known. This effect might reflect aluminum action either at the secretion level [11] or at the production level, as Díaz-Corte et al. [12] recently demonstrated. These authors have shown a decrease of mRNA of pre-proPTH in the parathyroid gland of rats with renal failure subjected to an acute aluminum load. What we would find in the bone biopsies of these patients is, in spite of all these considerations, an incognita.

It was also a surprise to find such a low correlation between iPTH and bAP even in those groups where, by definition, they should be in the ‘same range’, namely groups I and III. It would have been interesting to compare the histological results of these patients’ bone, in which case we might have identified different subgroups according to different levels of activation of osteoblasts and osteoclasts as it is recently being discussed. Indeed, Gal-Moscovici and Popovtzer [15] have recently reported on a new variant of ABD in which there is an increase of reabsorptive activity (traded by the presence of a rela-

<table>
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<tr>
<th>P</th>
<th>n</th>
<th>P, mg/dl</th>
<th>Ca, mg/dl</th>
<th>iPTH, pg/ml</th>
<th>bAP, ng/ml</th>
<th>Al, µg/l</th>
<th>r</th>
<th>p</th>
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<tbody>
<tr>
<td>≥ 7 mg/dl</td>
<td>66</td>
<td>8.13 ± 1.10</td>
<td>9.64 ± 0.91</td>
<td>631.0 ± 487.7</td>
<td>22.93 ± 17.42</td>
<td>10.16 ± 3.46</td>
<td>0.67</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;7 mg/ml</td>
<td>430</td>
<td>4.17 ± 1.37</td>
<td>9.17 ± 0.81</td>
<td>253.3 ± 191.6</td>
<td>20.44 ± 13.14</td>
<td>10.83 ± 4.40</td>
<td>0.30</td>
<td>&lt;0.001</td>
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tively high number of osteoclasts in the bone biopsy). They pointed to the possible role of \( \beta_2 \)-microglobulin in its etiopathogenesis as well as cytokines like TNF-\( \alpha \), interleukin-1\( \beta \) or interleukin-6. The patients with this variant, like all the others with ABD, showed low serum iPTH levels. Unfortunately the values of bAP in those patients, compared with the others with typical ABD, were not reported.

In conclusion, although iPTH and bAP are frequently in agreement (what makes bAP determination redundant), it is not always the case. Indeed, in particular circumstances, it seems important to separate parathyroid activity given by iPTH, from bone remodelling reflected by bAP. According to our results, this separation appears to be prominent in the presence of either a higher aluminum exposition or a well-controlled phosphatemia. Fortunately, the latter condition is becoming more frequent, thanks to both the use of newer phosphorus chelants and to the growing of dialytic efficacy. In this way, we advocate that the measurement of bAP and the biochemical characterization of bone turnover should be more frequently performed.

References


