Biochemical markers for non-invasive diagnosis of hyperparathyroid bone disease and adynamic bone in patients on haemodialysis

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Abstract The diagnostic and predictive value of serum intact parathyroid hormone (iPTH) and osteocalcin (bone Gla protein, BGP), alone or in combination, have been examined in only a small number of haemodialysis patients.

Methods. We studied prospectively 114 patients (46 women, 68 men; mean age 52 ± 12 years) on regular haemodialysis for a mean of 55 (6-185) months. All patients underwent labelled transiliac bone biopsy, and serum levels of iPTH, BGP and alkaline phosphatase were determined.

Results. Seventy-one patients (62%) showed histological findings of hyperparathyroid bone disease, 24 (21%) mixed bone disease, six (5.5%) osteomalacia and 13 (11.5%) adynamic bone. Bone aluminium deposition over more than 25% of the trabecular bone interface was found in 66 patients (58%). Serum iPTH and BGP correlated with the majority of histomorphometric indices of bone formation, mineralization and resorption (r > 0.5, P < 0.01). iPTH levels ≥ 200 pg/ml and BGP ≥ 50 ng/ml were found to be indicative of hyperparathyroid bone disease, whilst iPTH levels < 65 pg/ml and BGP < 20 ng/ml were indicative of adynamic bone. However, the positive predictive value of these indices was limited (less than 80%), although their negative predictive value, especially when used in combination, was good (more than 90%) and the exclusion of hyperparathyroid bone disease and adynamic bone was possible. The diagnostic and predictive value of these bone markers were improved when patients with bone aluminium deposition were excluded.

Conclusions. Diagnosis of hyperparathyroid bone disease and adynamic bone is difficult on the basis of iPTH and BGP, especially when bone aluminium deposition is prevalent. However, using these bone markers, preferably in combination, the exclusion of these lesions is feasible.

Key words: renal osteodystrophy; bone biopsy; adynamic bone; diagnostic and predictive value; intact parathyroid hormone; osteocalcin

Introduction

Renal osteodystrophy (ROD) is a common complication of end-stage chronic renal failure and maintenance dialysis treatment. It can be responsible for disabling symptoms and bone deformities and may also result in extraskeletal features such as vascular calcification. Now that more flexible dialysis regimes are available, accurate non-invasive diagnosis of the type of ROD would provide the ideal foundation on which to build an individually tailored management strategy for each patient (e.g. dosage and timing of vitamin D3 derivatives and phosphate binders as well as prescription of the appropriate concentration of calcium in dialysis fluid).

Although bone biopsy with tetracycline labelling remains the gold standard for diagnosis of ROD, it is not popular with either patients or physicians because of its invasive nature. Consequently the need for non-invasive diagnostic techniques has long been recognized.

Over the last 5 years various biochemical markers of bone metabolism have been proposed. The use of the immunoradiometric assay for the determination of intact parathyroid hormone (iPTH) was certainly an advance [1,2], and serum levels have been shown to correlate well with rate of bone turnover [3,4]. However, whilst iPTH values accurately represent circulating PTH levels, they only indirectly reflect bone metabolism [1]. Osteocalcin (bone Gla protein or BGP) is a unique bone protein synthesized exclusively by osteoblasts [5] and released into serum, where it accurately reflects osteoblastic activity and bone turnover [6,7].

BGP and iPTH serum levels have been evaluated in patients on dialysis and found to correlate with bone histomorphometry findings [8]. Their diagnostic value (sensitivity and specificity), either alone or in combination with other markers, has been reported in several studies [2,4,9-12], but only in relatively small groups
Non-invasive markers of renal osteodystrophy

of patients. Only one sizable study of their usefulness in predicting bone histology in a mixed group of peritoneal and haemodialysis patients has been reported [3].

Aims

To evaluate the correlation of BGP and iPTH with the histological findings in 114 maintenance haemodialysis patients, and to examine their individual and combined diagnostic and predictive values.

Subjects and methods

Patients

One hundred and fourteen consecutive patients, 46 females and 68 males, on regular haemodialysis treatment were included in this study. All patients had been on dialysis for at least 6 months at the time of the study, had not received desferrioxamine, pulses of vitamin D₃ or corticosteroids, and were free from hyper- or hypothyroidism. Eight patients had previously undergone parathyroidectomy but not within the preceding 2 years. Seven patients had previously undergone renal transplantation 2–3 years prior to the study. Vitamin D₃ derivatives were used in small doses (0.25–0.5 μg daily) in 39 (34%) patients. Twenty patients were referred to our centre from two other units because of clinical symptoms (bone pain, intractable pruritus) and biochemical data suggestive of ROD, but without iPTH determination. This self-selected group of patients did not skew the results and therefore was included. Other patients (94) were enrolled on a prospective non-selective basis, regardless of the presence of clinical signs and symptoms or biochemical features.

Mean age for the complete group was 52 ± 12 years, with a duration of dialysis of 55 (6–185) months. The mean predialysis duration of CRF (where known, n = 82) was 52 (12–94) months; 87 patients (76%) were on calcium based phosphate binders (carbonate or acetate), and six (5%) were on a combination of calcium salts with aluminum containing binders.

The underlying renal disease was chronic glomerulonephritis in 43%, chronic interstitial nephritis and obstructive nephropathy in 20%, ADPKD in 12%, diabetes mellitus in 8%, hypertensive nephropathy in 5%, and unknown renal disease in 12% of patients.

Informed consent was obtained from all patients and the Helsinki principles for clinical studies were followed.

Methods

Bone histomorphometry. Dual tetracycline-labelled bone biopsies were obtained from the anterior iliac crest under local anaesthesia with a Villargy-Zillerman needle. In almost all patients two adjacent biopsies of 5 mm diameter and 8 mm length were taken. Patients received doxycycline 100 mg twice daily for 3 days and then 10 days later the same dose was given for a further 4 days. The biopsy was performed 6–7 days after this dose. Patients were advised not to take any antacids or phosphate binders during the days on which they were taking tetracycline.

Specimens were fixed in ethanol, transported to the laboratory and processed as already reported [8]. The histomorphometric analysis was performed using a VIDS II image analyser. The following histomorphometric indices were calculated and expressed according to standard nomenclature [13].

I. Static
(a) Trabecular bone

Structural
1. Bone volume, BV/TVt (%)  
2. Wall thickness, WTh (μm)
3. Trabecular number, TbN (1/mm³)
4. Trabecular separation, TbSp (μm)
5. Trabecular thickness, TbTh (μm)

Formation
1. Osteoid volume, OV/BV(%)  
2. Osteoid surface, OS/BS(%)  
3. Osteoid thickness, OTh (μm)
4. Osteoblastic surface, ObS/BS(%)  

Resorption
1. Osteoclast number, Noc/TAr (1/mm²)
2. Osteoclastic surface, Ocs/BS(%)  
3. Eroded surface, ES/BS(%)  

Mineralization
1. Total mineralizing surface, MS(sLS + dLS)/OS(%)  
2. Mineralizing surface, MS(dLS + 1/2 sLS)/BS(%)  

(b) Cortical bone

1. Cortical thickness (μm)
2. Bone volume, BV/TVc(%)  
3. Wall thickness, WTh (μm)
4. Osteoclast number, Noc/CtAr (1/mm²)
5. Subcortical osteoclast number, Noc/BSs (1/mm²)

II. Dynamic

1. Trabecular appositional rate, TAR (μm/day)
2. Cortical appositional rate, CAR (μm/day)
3. Bone formation rate (BFR/BVt(dLS + 1/2 sLS)) (%/y)

Paratrabecular marrow fibrosis was semi-quantitatively graded from 0 to 4 (0, absence; 1, scanty wisps of fibrous tissue; 2, thin bands of fibrous tissue at less than 50% of trabecular surfaces; 3, thick bands over more than 50% of trabecular surfaces; 4, thick bands over 95–100% of trabecular surfaces, plus replacement of marrow spaces by central fibrosis).

Aluminium was stained by acid solochrome azurine and, if present, was expressed as a percentage of trabecular–osteoid interfaces. Perls' stain was used to exclude cross-reaction with iron deposits.

Histomorphometry findings were classified into four groups on the basis of our previously reported normal values [14].

Hyperparathyroid bone disease: characterized by increased osteoblastic, osteoclastic and eroded surfaces, high or normal mineralization fronts and high or normal bone formation rate. Osteoclast and osteoblast number was increased. Paratrabecular fibrosis was typically found and resorption tunneling might be present.

Osteomalacia: characterized by increased volume, thickness and surface of osteoid, and reduction or absence of mineralization with reduced bone formation rate. Adynamic bone: characterized by reduced numbers of bone cells, absence of active remodelling sites and mineralization fronts, with very low bone formation rate.

Mixed ROD: characterized by increased osteoid surfaces and thickness. Areas of increased osteoblastic and osteoclastic activity and paratrabecular fibrosis coexisting with patchy (focal) areas of mineralization defect, and with variable formation rate.

Biochemical parameters. Blood samples for biochemical examinations were taken on the day of bone biopsy at
between 8.30 and 9.30 a.m. They were transported to the laboratory and centrifuged within 15 min, then stored at 
-20°C. The samples were defrosted once only for determination of iPTH by immunoradiometric assay (Nichols Allegro; normal range 10–65 pg/ml) and BGP by radioimmunoassay (Cis Diagnostics; using polyclonal bovine antibodies; normal range 5–13.5 ng/ml). Mean values of at least two sequential measurements (within 6 months) are reported.

Intra- and inter-assay variation of the above methods was less than 7 and 8%, respectively.

Total alkaline phosphatase (normal range 39–117 iu/l), calcium (8.5–10.5 mg/dl) and phosphorus (2.5–4.5 mg/dl) were determined using standard colorimetric methods. Serum calcium was corrected (cCa) for serum albumin according to the formula cCa (mg/dl) = serum calcium (mg/dl) + 0.8 x (4.5–serum albumin (mg/dl)).

Statistical analysis. Results are reported as mean ± SD unless otherwise stated. The distribution of all variables was examined and appropriate statistical methods chosen. Group differences were examined with χ2 and Kruskal–Wallis ANOVA median test (non-continuous discrete or not normally distributed variables) or Student’s t test and one-way ANOVA (for variables with normal distribution).

The possible relationship between biochemical and histological parameters was examined by linear correlation (Pearson’s) and non-parametric correlation (Spearman’s) as appropriate. All biochemical markers found to correlate significantly with the histomorphometric parameters were examined by stepwise multivariate regression in order to identify the most important marker.

The diagnostic value of each biochemical marker was evaluated in terms of sensitivity (true positives as a percentage of patients with the particular histological type of ROD), specificity (true negatives as a percentage of patients without this particular histological type of ROD), the likelihood ratio (LR) (probability that a patient with a positive result has the disease compared to ones in whom the result was negative) and Youden’s index (sensitivity + specificity – 1)). The predictive value of the markers was assessed according to Bayes’ theorem [15] using the probability of the bone lesion being present if the test result is positive, that is positive predictive value (PPV), and the probability of the lesion being absent if the test result is negative, that is negative predictive value (NPV). Relevant calculations are given in the appendix. Receiver operating characteristic (ROC) curves were employed to choose the most useful threshold levels for biochemical markers.

Results

Bone histology

Seventy-one patients (62%) were found to have hyperparathyroid bone disease. Twenty-four patients (21%) had mixed ROD, 13 (11.5%) adynamic bone and six patients (5.5%) osteomalacia. There were no significant differences among the patients with different bone lesions in terms of their age, underlying renal disease, the duration of predialysis chronic renal failure or time on haemodialysis (Table 1).

Aluminium deposition was found in 66/114 (58%) of patients. Of the patients with hyperparathyroid bone disease, 44% (31 patients) showed aluminium deposition. Aluminium was deposited at 25–50% of the bone–osteoid interface in 20 of these patients (30%), at 50–75% in 15 (23%), and at more than 75% in the remaining 31 patients (47%) reaching in some cases 100% of the bone–osteoid interface. Aluminium deposition was more common (χ2 = 5.6, P = 0.02) in patients with other types of ROD, that is in 20 (83%) of the patients with mixed osteodystrophy, in nine (69%) with adynamic bone, and in all six patients (100%) with osteomalacia.

Hyperparathyroid bone disease was more common in women than men, with indices of turnover, such as bone formation rate, osteoclast number, and mineralizing surface being significantly higher (P < 0.05).

Biochemical parameters and histological types of ROD

The mean values and standard deviations of all biochemical parameters in the various types of ROD are presented in Table 2. BGP, iPTH, and ALP values

### Table 1. Clinical characteristics of patients with different histological types of renal osteodystrophy

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>Hyperparathyroid bone disease</th>
<th>Mixed ROD</th>
<th>Adynamic bone</th>
<th>Osteomalacia</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (female, %)</td>
<td>52</td>
<td>24</td>
<td>16</td>
<td>0</td>
<td>0.007</td>
</tr>
<tr>
<td>Age (years)</td>
<td>54.5 ± 11.8</td>
<td>57.1 ± 8.8</td>
<td>53.9 ± 17.1</td>
<td>53.5 ± 10.3</td>
<td>NS</td>
</tr>
<tr>
<td>Duration on HD (months)</td>
<td>56.6 ± 46</td>
<td>40.2 ± 35</td>
<td>62 ± 50</td>
<td>81 ± 67</td>
<td>NS</td>
</tr>
<tr>
<td>Duration of CRF (if known)</td>
<td>59 ± 40</td>
<td>63.9 ± 54</td>
<td>81 ± 75</td>
<td>93.7 ± 34</td>
<td>NS</td>
</tr>
</tbody>
</table>

### Table 2. Biochemical parameters in patients with different histological types of renal osteodystrophy

<table>
<thead>
<tr>
<th>Biochemical parameter</th>
<th>Hyperparathyroid bone disease</th>
<th>Mixed ROD</th>
<th>Adynamic bone</th>
<th>Osteomalacia</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>iPTH (pg/ml)</td>
<td>621 ± 451</td>
<td>397 ± 393</td>
<td>152 ± 114</td>
<td>139 ± 125</td>
<td>0.0006</td>
</tr>
<tr>
<td>BGP (ng/ml)</td>
<td>103 ± 67</td>
<td>68.2 ± 50</td>
<td>24 ± 19</td>
<td>47 ± 29</td>
<td>0.0006</td>
</tr>
<tr>
<td>ALP (iu/l)</td>
<td>183 ± 115</td>
<td>186 ± 134</td>
<td>75 ± 26</td>
<td>103 ± 286</td>
<td>0.01</td>
</tr>
<tr>
<td>Ca (mg/dl)</td>
<td>9.1 ± 0.8</td>
<td>9.1 ± 0.6</td>
<td>9.5 ± 1.1</td>
<td>9.4 ± 1.4</td>
<td>NS</td>
</tr>
<tr>
<td>P (mg/dl)</td>
<td>7.6 ± 1.1</td>
<td>7.6 ± 1.2</td>
<td>6.9 ± 1.8</td>
<td>5.8 ± 0.9</td>
<td>NS</td>
</tr>
</tbody>
</table>
Non-invasive markers of renal osteodystrophy varied significantly between the groups, whereas serum calcium and phosphorus values were similar. iPTH and BGP values (both absolute values and after transformation) did not correlate with age or gender.

iPTH values showed a considerable overlap among the different groups (Figure 1) which was more pronounced than the overlap in BGP values (Figure 2). Moreover, discriminant analysis showed that BGP was able reliably to categorize the patients into the various histological groups (partial lambda 0.79, P<0.001), whereas iPTH was not. ALP values also showed a large overlap among the different groups (Figure 3).

**Correlations of iPTH, BGP and ALP**

Table 3 shows the correlations of histomorphometric indices with serum levels of iPTH, BGP and ALP. ALP only correlated with osteoid volume, but iPTH and BGP showed good correlations with all three dynamic indices as well as indices of bone formation, resorption and mineralization.

In addition, multivariate analysis was performed to identify the main determinant among iPTH, BGP and ALP for each histomorphometric index. This
demonstrated that BGP was the most important predictor of indices of mineralization and formation, and also of some indices of bone resorption, whereas iPTH was the main determinant of osteoclast number, cortical thickness, and degree of paratrabecular fibrosis.

Diagnostic and predictive value of iPTH, BGP, and ALP

In mixed ROD, iPTH and BGP values showed wide variations and it was not possible to select threshold levels. Values in patients with OM could not be tested because of the small numbers. Serum total ALP was found to be of limited diagnostic value in all of the groups (low sensitivity and specificity).

ROC curves with six threshold levels for iPTH and BGP, and three for ALP for the diagnosis of hyperparathyroid bone disease are shown in Figure 4. iPTH > 200 pg/ml, BGP > 50 ng/ml and ALP > 100 IU were the most useful threshold levels. ROC curves for adynamic bone are not shown because of the small number of patients. Using these threshold levels the

diagnostic and predictive value of iPTH and BGP for the different bone lesions was assessed and the results are presented in Table 4.

iPTH, BGP and ALP in patients without bone aluminium deposition. When the patients with bone aluminium deposition were excluded, the prevalence (%) of histological types of bone disease was different in the remaining patients. Hyperparathyroid bone disease was more common (84%, 40 patients), mixed osteodystrophy and adynamic bone were rare (8%, 4 patients each) and osteomalacia was totally absent. The usefulness of serum ALP was not improved in any of the groups, but the diagnostic and predictive value of iPTH and BGP in hyperparathyroid bone disease were increased as shown in Table 5 and Figure 5 with ROC curves. The small number of patients with adynamic bone without aluminium deposition (n = 4) precludes analysis.

Discussion

This study of 114 patients represents almost the 3.5% of the total population of registered haemodialysis

<table>
<thead>
<tr>
<th>Table 4. Diagnostic and predictive value of iPTH and BGP for hyperparathyroid bone disease and adynamic bone</th>
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</thead>
<tbody>
<tr>
<td>Threshold levels</td>
</tr>
<tr>
<td>Hyperparathyroid bone disease</td>
</tr>
<tr>
<td>n = 71</td>
</tr>
<tr>
<td>iPTH &gt; 200 or BGP &gt; 50</td>
</tr>
<tr>
<td>Adynamic bone</td>
</tr>
<tr>
<td>n = 13</td>
</tr>
<tr>
<td>iPTH &lt; 65 or BGP &lt; 20</td>
</tr>
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</table>

Sens, sensitivity; Spec, specificity; YI, Youden index; LR, likelihood ratio; PPV and NPV, positive and negative predictive value; 95% confidence limits in parentheses.
patients in Greece [16]. Their clinical and demographic characteristics are similar to the available demographic data of Greek patients from the most recent national and EDTA records [17]. Therefore there is good reason to suggest that our patients are representative of the whole population of Greek haemodialysis patients.

The majority of our patients suffered from hyperparathyroid bone disease and only a small number of patients had adynamic bone, in agreement with reports from other European countries [4,18,19]. However, this distribution is completely different from that reported by Sherrard et al. [20] from North America and Torres from Canary Islands [11] who found adynamic bone in approximately one-third of their haemodialysis patients.

Bone aluminium deposition was very common in our patients, and requires explanation. A high prevalence of aluminium deposition was also reported by Memmos et al. [21] (31%) and Lemoniatou et al. [22] (59%) from two other Greek centres. However, serum aluminium levels are known to be declining in many units [23]. Acid solochrome azurine stain for aluminium is more sensitive than the conventionally employed tricarboxylic acid (Aluminon) [24], and Romanski et al. [25] were able to identify 40% more positive patients with it than with Aluminon. However, the prevalence of aluminium was found to be low in the Manchester area by Hutchison et al. [4], who use the same stain by the same laboratory; therefore we feel confident that this alone does not explain the higher incidence of aluminium deposition in this study. Given that the water is treated by reverse osmosis or deionization, only the ingestion of aluminium-containing phosphate binders, which has been dramatically reduced only within the last 4–6 years, can explain the high prevalence of aluminium deposition in our patients. In fact deposition was less marked in patients who started dialysis after 1989 (35%) compared to those starting in the previous years (66%). Therefore previous aluminium overload may be responsible, as suggested by Malluche and Monier-Faugere [26], who also found a high prevalence of aluminium deposition in the US.

Surprisingly, aluminium deposition was encountered in 44% of the patients with hyperparathyroid bone disease, both deep within bone, and also heavily deposited at the critical bone–osteoid interface, where it is thought to impair bone formation and mineralization [27]. However, similar findings were reported by Cournot-Witmer et al. [28] who suggested that in such aluminium-intoxicated patients, secondary hyperparathyroidism may prevent the aluminium-induced mineralization defect.

As we have previously reported [29], no correlation could be found between aluminium deposition and histomorphometric indices of bone formation, and no effect of aluminium was evident on osteoblast or osteoclast response to iPTH, although in patients with adynamic bone but inappropriately high iPTH levels, the depressive effect of aluminium [30] would still seem to be the only likely explanation for the low bone turnover rate.

The preponderance of hyperparathyroid bone disease in women cannot be explained on the basis of differences in age, duration of dialysis or previous CRF, underlying renal disease, or higher iPTH levels, since the two groups of patients were comparable in all these respects. Moreover, as we have previously reported [31], histomorphometric indices of bone formation and bone response to similar iPTH levels appear higher in women than in men, even after adjusting for all confounding parameters. Of our female patients, 80% were older than 50 years, amenorrhoeic, and possibly oestrogen deficient. The antiresorptive effect of oestrogen has been well established in women with normal renal function [32] and there are data both in rats [33] and humans [34] suggesting a similar effect in uraemia. Therefore, lack of oestrogen and consequent bone susceptibility to parathyroid hormone is an attractive explanation. Female gender as a separate identifiable risk factor for bone disease has been suggested by other authors, although without histological confirmation [35,36].

BGP showed a significant correlation with histomorphometric indices of bone formation and mineralization. This confirms, in a large number of patients, the previous report by Malluche et al. [37], who studied 30 patients on HD and found that BGP is a good marker of osteoblastic activity. However, the peculiar correlation of BGP with histomorphometric indices of osteoblastic activity may be partly explained by the coupled relationship between osteoblastic and osteoclastic activity that usually exists in hyperparathyroid bone disease. Another possible explanation is the heterogeneity of the detected serum BGP molecules. Our assay detects not only intact BGP, which is probably derived directly from osteoblastic synthesis, but also BGP fragments released during osteoclastic resorption...
of bone matrix [38]. Consequently, serum BGP may inappropriately reflect also the osteoclastic activity. The recently introduced immunoradiometric assay for determination of intact BGP, similar to the one used for iPTH determination, may be more accurate since it does not measure BGP fragments [39].

In our patients with hyperparathyroid bone disease, the values of iPTH showed a wide scatter (Figure 1) and this was not due only to the range of severity of the bone lesion, since severe hyperparathyroid bone disease was encountered at relatively 'normal' serum iPTH values. iPTH and BGP alone were of limited diagnostic value. iPTH showed only moderate sensitivity as a result of nine patients with histological hyperparathyroid bone disease having iPTH levels < 200 pg/ml. It is noticeable that nearly all of them (8/9) were female and this is in line with the previous observation that bone response to iPTH is more marked in women than in men. The specificity of iPTH in the diagnosis of hyperparathyroid bone disease was very low and could not be substantially improved even when high values (> 500 pg/ml) were chosen as threshold levels (Figure 4).

BGP showed high sensitivity in the diagnosis of hyperparathyroid bone disease but unacceptably low specificity, since 19 of the 19 patients without hyperparathyroid bone disease had BGP levels > 50 ng/ml, most of them having a mixed type of histological lesion.

Active hyperparathyroid bone disease can be present with iPTH levels ≤ 200 pg/ml particularly in women. In these cases the determination of BGP levels might be helpful, since it is likely to be high (above 50 ng/ml). When iPTH and BGP levels were used in combination, a considerable increase in sensitivity was achieved but at the expense of specificity. However, the NPV rose to 90%, meaning that patients with BGP levels lower than 50 ng/ml and iPTH levels lower than 200 pg/ml, have only a 10% probability of having hyperparathyroid bone disease. Nevertheless, this means that the combination of these two markers would misdiagnose 10% of cases who might therefore receive inappropriate treatment.

In adynamic bone the sensitivity of iPTH was low, since four patients with the lesion had iPTH levels ≥ 65 pg/ml (all of these had severe bone aluminium deposition). On an individual basis, the sensitivity of iPTH and BGP alone or in combination was good, but the PPV was poor. This disappointing result is a statistical effect of the low prevalence of adynamic bone in our patients. According to Baye's theorem, the clinical value of each biochemical parameter is strongly influenced by the prevalence of disease in the same population (see Appendix for calculations). Since the sensitivity, specificity, and likelihood ratio are high, the PPV would be dramatically better in populations where the prevalence of adynamic bone is high. Although the pathological significance of adynamic bone remains unclear many centres are 'treating' it by reducing dialysis fluid calcium and attempting to stimulate iPTH and increase bone turnover. Before doing this it would be important to be sure of the diagnosis, and in our patients it appears that only bone biopsy would allow this.

iPTH alone was not able to distinguish adynamic bone from hyperparathyroid bone disease. Qi et al. [10] reported poor specificity of iPTH in 45 haemodialysis and 34 CAPD patients. Values of iPTH < 450 pg/ml in haemodialysis and < 600 pg/ml in CAPD patients were not specific for high bone turnover. Our findings are similar, and we found that iPTH values of 2–3 times normal may not ensure acceptable bone histology, as suggested previously by other studies where iPTH was found to be more specific [8,40,41]. The high incidence of bone aluminium deposition in our study and (to a lesser extent) in that of Qi et al. may be the explanation of this contradiction. The diagnostic value of the biochemical markers, especially that of iPTH, improved when patients with bone aluminium deposition were excluded, and became comparable to the figures of Wang et al. in 66 haemodialysis patients without bone aluminium deposition [3].

In a study in which three assays for parathyroid hormone were compared, Cohen-Solal et al. [2] reported that iPTH failed to discriminate between adynamic bone and moderate hyperparathyroid bone disease. Monier-Faugere and Malluche [42] found high iPTH levels in patients with adynamic bone and therefore it is reasonable not to rely solely on iPTH levels. However, Mazzafaro et al. [9] did not have the same difficulty in distinguishing adynamic bone from hyperparathyroid bone disease using C terminal PTH alone, and did not find BGP of additional value. Charhon et al. [8] found that serum BGP discriminated high and low turnover better than ALP, but comparison with iPTH was not reported. Such discrepancies may be explained by differences in the assay employed for parathyroid hormone, the differing prevalence of high and low turnover, and the prevalence of aluminium deposition as mentioned above. Differences in cut-off levels and definitions also confound comparison of different studies. In 24 asymptomatic dialysis patients Cohen-Solal et al. [2] showed that when iPTH and BGP were both required to be above or below certain cut-off values, specificity improved modestly at the expense of sensitivity. If threshold levels of iPTH or BGP were used as in our study, sensitivity is increased at the expense of specificity. Using combinations of the iPTH and BGP threshold values, as determined by ROC curves, we noticed that the increase achieved in specificity and PPV was modest, whereas the increase in sensitivity and NPV was more pronounced and is probably more clinically important.

A number of our patients with adynamic bone plus heavy aluminium deposition had high iPTH levels. This is in contrast with the results of Hutchison et al. [4] and Hercz et al. [43] who found that adynamic bone was associated with relatively low iPTH levels. It is likely that the heavy aluminium deposition in our patients was responsible for the development of adynamic bone, regardless of the high iPTH levels. This probably is the reason why iPTH was a poor indicator
of adynamic bone in our patients. However, in most of these cases BGP levels were less than 20 ng/ml and we suggest that BGP is a better marker of bone turnover in the presence of aluminium deposition. This would be expected on theoretical grounds since BGP is produced directly by bone cells, whereas iPTH is an indirect marker. Despite this, combined use of iPTH and BGP levels did not result in a significant improvement in PPV. However, the NPV was improved markedly by combined use of these two markers (Table 5), so that in patients with iPTH values \( \geq 65 \) pg/ml and BGP \( \geq 20 \) ng/ml one can say with 99% certainty that they do not have adynamic bone. Unfortunately this does not necessarily mean that the patients have hyperparathyroid bone disease, since one cannot exclude the possibility of OM or mixed ROD.

Basal and DFO stimulation aluminium tests were not used in this study. However, as Pei et al. [44] showed, these tests are not reliable in predicting the aluminium deposition in patients who had discontinued aluminium-containing phosphate binders more than 6 months previously, which was the case in the majority of our patients. In such patients only bone biopsy can accurately quantify aluminium burden, and this is especially important prior to parathyroidectomy, which might otherwise cause severe hypoparathyroidism and low bone turnover.

In conclusion, we suggest that in centres known to have a high prevalence of aluminium deposition the diagnostic value of iPTH is likely to be poorer than that in previously reported studies. In such centres we recommend;

(a) If a patient has high iPTH levels but low BGP then the diagnosis of hyperparathyroid bone disease is doubtful and the patient may in fact have severe aluminium toxicity with secondary adynamic bone.

(b) If a patient with low to normal iPTH has a high BGP, adynamic bone is less likely, and especially in women suspect hyperparathyroid bone disease. Do not stimulate iPTH secretion by lowering dialysate Ca, since this may worsen underlying hyperparathyroid bone disease.

(c) If both iPTH and BGP levels are high, hyperparathyroid bone disease is the most likely diagnosis but in the presence of aluminium a mineralization defect is common and mixed ROD may be present.

We conclude that in our population iPTH and BGP, alone or in combination, do not enable positive diagnosis of type of ROD, but can reliably exclude hyperparathyroid bone disease or adynamic bone, even in the presence of heavy aluminium deposition. Where iPTH and BGP are contradictory one should suspect aluminium deposition, and a bone biopsy is probably necessary to enable a diagnosis to be reached if it is thought clinically important to do so.

References

**Appendix**

**Calculations**

Youden's index: sensitivity × (specificity - 1).

Positive predictive value =

(sensitivity × prevalence)/(sensitivity × prevalence) + (1 - specificity) × (1 - prevalence).

Negative predictive value =

sensitivity × (1 - prevalence)/(1 - sensitivity) × prevalence + specificity × (1 - prevalence).

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