Renal bone disease in 76 patients with varying degrees of predialysis chronic renal failure: a cross-sectional study

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Abstract

Background. Renal osteodystrophy has been studied less extensively in predialysis than in dialysis patients. Different types of histological patterns in their natural evolution from moderate to advanced severity of renal insufficiency are only partially known, with special regard to adynamic bone disease and its relationship with osteomalacia.

Methods. We conducted a cross-sectional retrospective study on 76 unselected patients with chronic renal failure undergoing conservative treatment, with a wide range of severity of renal insufficiency. All the patients were subjected to bone biopsy for histological and histomorphometric evaluation. The patients, 44 males and 32 females ranging in age from 18 to 72 years and with serum creatinine 1.2-11.4 mg/dl, had not been exposed to aluminium-containing drugs and had never been treated with vitamin D or calcitriol.

Results. Ten patients had normal bone, nine were diagnosed with adynamic bone disease, 26 with mild mixed osteodystrophy, seven with predominant osteomalacia, 22 with advanced mixed osteodystrophy, and two with predominant hyperparathyroidism. Patients with adynamic bone disease had less severe chronic renal failure than the other pathological subgroups, intact PTH above the upper limit of normal, normocalcaemia, and reduced serum osteocalcin in line with a significantly lower ObS/BS.

Osteomalacia was found in a more advanced stage of chronic renal failure with relative hypocalcaemia and more severe metabolic acidosis. A creatinine clearance of 20 ml/min served as a clear demarcation between this histological group and adynamic bone disease.

Conclusions. It is postulated that adynamic bone disease is a form of renal osteodystrophy, separate from osteomalacia, appearing when bone resistance to PTH develops, probably a transient stage to more advanced hyperparathyroid histological classes with increasing severity of chronic renal failure.

Key words: renal osteodystrophy; end-stage renal disease; non-dialysed patients; bone histomorphometry; adynamic bone disease; osteomalacia; secondary hyperparathyroidism; PTH resistance.

Introduction

Predialysis renal failure, when not accompanied by vitamin D treatment or administration of aluminium or calcium-containing phosphate binders, allows for the evaluation of the natural course of renal bone disease without the confounding variables that are frequently present in the dialysis population [1]. The occurrence of renal bone disease beginning in the early stages of renal insufficiency has been known for many years [2], but the prevalence of different types of bone disease associated with the various stages of chronic renal failure is less established [3-6]. Osteomalacia has been reported as a rare condition [3]. Adynamic bone disease has been studied in patients mainly in end-stage renal failure and found to occur rather frequently [5-7]. This study evaluates the prevalence and presumptive stage of appearance of different forms of renal bone disease, in order to speculate on the natural evolution of the disease.

Subjects and methods

A retrospective evaluation of a series of patients with various degrees of chronic renal failure, but not yet undergoing renal replacement therapy was performed. The subjects were from the out-patient clinic of the Inst. of 2nd Clinica Medica, Nephrology Service, who underwent a bone biopsy for evaluation of bone disease. Seventy-six patients with chronic renal failure with serum creatinine ranging from 1.2 to 11.4 mg/dl (5.23 ± 2.55 mg/dl), creatinine clearance 19.54 ± 11.87 ml/min, age 18-72 years, and consisting of 44 males and 32 females, were considered. The body mass index
and serum albumin were respectively 24.6 ± 3.1 (18.3–33.9) and 3.89 ± 0.74 g/dl (M ± SD).

The causes of renal failure were chronic glomerulonephritis (CGN) in 43 patients, tubulointerstitial nephritis (TIN) in 16, polycystic kidney disease (PKCD) in seven, medullary cystic disease (MCD) in one, and were unknown in nine patients. Eleven patients were affected by non-insulin-dependent diabetes mellitus. All the patients were subjected to several biochemistry determinations as part of a routine study, which included serum calcium, phosphate, alkaline phosphatase, intact PTH, C-terminal PTH, osteocalcin, creatinine, and bicarbonate. After informed consent, they were also subjected to transiliac bone biopsy for histology, aluminium histochemistry, histomorphometry, and histodynamic studies following a double course tetracycline administration.

At the beginning of the follow up, all patients were placed on a moderately restricted protein diet (0.8 g/kg bw/day; 75% HBV) and phosphate (12 mg/kg bw/day), with a caloric content of 30–35 kcal/kg bw/day. Because of the low calcium content of the diet, the patients received daily calcium supplementation of 500 mg p.o. as a mixture of lactate, carbonate, and gluconate. There was no need for vitamin D supplementation, since the diet was adequate in vitamin D and all the patients received normal sun exposure. This was confirmed by the normal levels of serum 25, OHD3 (25.8 ± 12.8 ng/ml, range 7.0–59.4) found which is in agreement with published data [8]. None of the patients had been treated with corticosteroids in the previous 12 months. None received anticoagulant and anticonvulsive medicaments or non-steroidal anti-inflammatory drugs. None of them had ever been on vitamin D or calcitriol administration, or on non-steroidal anti-inflammatory drugs. None of them had hypothyroidism. After a period of follow-up of 8–24 months, transiliac bone biopsies were performed in all patients with a BORDER trocar, 5 mm internal diameter. In 48 patients, the biopsy was taken following double tetracycline administration (Rolitetracyclin, 150 mg i.m. twice daily for 2 days each course) with a 2-week interval. The bone sample was used for the evaluation of aluminium histochemical staining and for histological, histomorphometric and histodynamic examination. At the same time, blood samples for the determination of serum variables were drawn and immediately processed, or stored at −30°C until assayed.

Serum C-term iPTH was assayed with a radioimmunoassay method which uses a chicken antibody directed against the C-term (65–84) fragment of the human molecule. Intra- and interassay variations were 4.0 and 11.3% respectively. Normal mean value is 0.30 ± 0.16 ng/ml.

Serum intact iPTH was measured with a commercial kit (Incastar, Stillwater, USA) which uses an immunoradiometric method based on a double antibody technique. Intra- and interassay variations were 6.5 and 9.8% respectively. Normal mean value is 20.8 ± 7.43 pg/ml.

Serum osteocalcin, or BGP, was measured by radioimmunoassay based on the method of Price and Nishimoto [9]. The intra- and interassay variations were less than 5 and 8% respectively. Normal mean value is 3.89 ± 1.45 ng/ml.

Serum total calcium was assayed by atomic absorption spectrophotometry (Perkin Elmer, model 2380, Norwalk, CT; normal values, 8.8–10.5 mg/dl). Serum creatinine and phosphate were measured by autoanalyzer (Technicon Autoanalyzer RA 1000, Tarrytown, NY). The normal ranges for serum creatinine and phosphate are 0.5–1.1 and 3.0–4.5 mg/dl respectively. Alkaline phosphatase measurements were performed spectrophotometrically using p-nitrophenyl-phosphatase as the substrate (Boehringer-Biochemia, Mannheim, Germany). The normal range for the adult population is 35–125 mU/ml. Serum bicarbonate was measured with a gas analyser (ABL 30, Radiometer, Copenhagen).

Bone specimens were fixed in 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.2). They were then longitudinally halved, dehydrated in acetone and embedded without decalcification, using the JB-4 glycol-metacylate embedding mixture (Polysciences, Inc., Warrington, PA), as previously described [10]. Sections were cut on a Reichert–Jung Autocut microtome equipped with a tungsten carbide knife. Three 4-μm thick sections were stained by the aluminium histochemical staining technique [11]. Alternate sections, 1–2 μm thick, were stained with azure II-methylene blue for histomorphometric measurement of structural and static variables. Alternate sections, about 5 μm thick, were also prepared unstained to be examined under UV light for histodynamic evaluation of tetracycline fluorescent labels. Histomorphometric and histodynamic measurements were obtained using an interactive colour video-based Image Analysis System (IAS 2000, Delta Sistemi, Rome Italy) with a personalized software developed for bone histomorphometry. The following variables were measured [12]: bone volume (BV/TV, %), percentage of whole trabecular bone volume occupied by calcified and uncalcified bone tissue; osteoid volume (OV/BV, %), percentage of bone volume consisting of osteoid; osteoid thickness (OTh, μm), thickness of osteoid seams; osteoid surface (OS/BS, %), percentage of trabecular surface covered by osteoid; osteoblast surface (ObS/BS %), percentage of trabecular surface covered by osteoid lined by active osteoblasts; eroded surface (ES/BS, %), percentage of trabecular surface consisting of Howship lacunae; osteoclastic surface (Os/BS, %), percentage of trabecular surface covered by osteoclasts and undergoing resorption; single-labelled surface (sLS/BS, %), the extent of tetracycline single-labelled surface in percentage of trabecular surface; double-labelled surface (dLS/BS, %), the extent of tetracycline double-labelled surface in percentage of trabecular surface; mineralizing surface (MS/OS, %), the extent of double-labelled plus half the extent of single-labelled, in percentage of osteoid surface; mineral apposition rate (MAR, μm/day), the distance between the midpoints of two consecutive labels, divided by the time interval between the midpoints of the two labelling periods; bone formation rate, (BFR/BS, μm2/μm2/day), the volumetric amount of new mineralized bone per unit of trabecular bone surface per day; adjusted appositional rate (Aji.AR, μm/day), the mineral apposition rate over the entire osteoid surface; and mineralization lag time (ML, days), the mean time interval between deposition of osteoid matrix and its mineralization. Structural variables were evaluated at objective magnification of 2.5× and static and dynamic variables were evaluated at objective magnification of 10× [13]. Normal values (Table 1) for the histomorphometric parameters were determined from 88 subjects [14]. Normal histodynamic values from seven subjects are also reported in the Table.

Bone pathology was classified as predominant hyperparathyroidism (HP), predominant osteomalacia (OM), mild mixed (ostomalacia and hyperparathyroidism) osteodystrophy (MOMO), advanced mixed osteodystrophy (AMO), adynamic bone disease (ABD) and normal bone (N). The classification was made on the basis of morphological criteria from histomorphometric and histodynamic variables.
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Table 1. Causes of renal failure and cases with diabetes mellitus in the histological classes

<table>
<thead>
<tr>
<th>n</th>
<th>CGN</th>
<th>TIN</th>
<th>PCKD</th>
<th>MCD</th>
<th>Unknown</th>
<th>DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>HP</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AMO</td>
<td>22</td>
<td>12</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>OM</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>MMO</td>
<td>26</td>
<td>15</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>ABD</td>
<td>9</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>N</td>
<td>10</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

according to Malluche and Faugere [1]. In patients with normal bone, remodelling features were within normal range. The designation of predominant hyperparathyroidism implied a general increase in bone turnover rate and predominant osteomalacia was characterized by a decrease in bone turnover rate associated with an increase of both osteoid surface and thickness. In mixed osteodystrophy, local increase in bone turnover rate coexisted with defective mineralization and adynamic bone disease was characterized by reduced bone turnover with thin osteoid seams, bone cell paucity, and a decrease in tetracycline uptake. In the cases in which tetracycline labels were not available, histological diagnosis was based on the static histological features [15].

Statistical evaluation was carried out with two-way ANOVA and non-parametric tests such as Friedman’s and Wilcoxon’s tests. Multiple comparison of differences between histological classes was made with Bonferroni’s method [16].

Results

The histological and histomorphometric examination resulted in the identification of the following osteodystrophic subgroups: 10 patients had normal bone histo-

logically, nine had adynamic bone disease, 26 patients were classified as mild mixed osteodystrophy, 22 patients had features indicative of advanced mixed osteodystrophy, seven patients had predominant osteomalacia and only two patients had predominant hyperparathyroidism. The causes of CRF and diabetes mellitus in the different histologic classes are reported in Table 1. None of the patients had histochemical evidence of aluminium accumulation. Age, sex composition, and average values of the humoral and histomorphometric and histodynamic parameters for each group are reported in Table 2, together with the results of the ANOVA and average normal values for each parameter. Some of the most relevant parameters are shown in Figure 1 and Figure 2. The hyperparathyroid group, consisting of only two patients, was excluded from the statistical evaluation. The groups were not different with respect to age. Differences observed with ANOVA for all the humoral and most of the histomorphometric parameters were highly significant. The average values of serum creatinine progressively increased starting from normal bone to pure hyperparathyroidism through ABD, mild mixed osteodystrophy, osteomalacia, and were highest in patients with advanced mixed osteodystrophy. The same was observed for C-term and intact iPTH; the lowest values, at the upper level of normal, were found in patients with normal bone and the highest in the hyperparathyroid patients. Serum BGP was lower in the ABD group, than in the normal bone patients, and the level of BGP increased in the different pathological groups, with the highest levels in the hyperparathyroid patients.

Differences in the humoral and histomorphometric parameters were evaluated according to Bonferroni’s method [16]. Despite the small number of patients, there were significant differences in some humoral and in many histomorphometric and histodynamic parameters among histological groups (Table 3).

Evaluation of the creatinine clearances of the dia-
Fig. 2. Average values with standard deviations of pertinent histomorphometric and histodynamic parameters. Standard deviations are the numbers above the columns. Number of patients for each variable and significance of the differences are reported in Tables 2 and 3.

gnostic groups showed a significant difference (ANOVA, \( p < 0.0006 \)). Significant differences were observed between group N with normal bone histology, and groups OM (\( p < 0.05 \)), AMO (\( p < 0.01 \)), and MMO (\( p < 0.05 \)) respectively. ABD seems to be a transition group between the other pathologic classes and group N. This is also suggested by examination of the data from group OM and ABD. Using a cut-off level of 20 ml/min for creatinine clearance, a significant difference (\( p < 0.054 \)) was found between these two groups and a similar evaluation carried out between groups AMO and ABD resulted in \( p < 0.015 \), according to Fisher's test [16]. With respect to the OM and ABD groups, this cut-off is 85.7% sensitive and 66.7% specific (positive predictive value 67%, negative predictive value 86%) and for groups AMO and ABD, sensitivity and specificity are 81.8% and 66.7% respectively (positive predictive value 86%, negative predictive value 60%). Due to the low number of cases in the groups, these values are of orientative nature.

Serum calcium was normal in patients with normal bone and ABD, while it was lower in the OM (NS) and AMO (\( p < 0.07 \)) groups. Serum bicarbonate was normal in patients with normal bone and was decreased in the other groups. The lowest levels were found in OM patients, with values significantly lower (\( p < 0.01 \)) than in normal bone patients. Patients with normal bone had, on average, a serum intact PTH level lower than all the other histological groups. In particular, in spite of a significantly lower ObS/BS, the mean intact PTH value was higher (NS) in ABD than in normal bone patients, eventhough a large overlap of values existed. The difference between intact PTH of ABD and the other pathological groups was not significant. Serum BGP was significantly different between ABD and advanced mixed and mild mixed osteodystrophy groups. Normal bone patients differed significantly in mean serum BGP from the group with advanced mixed osteodystrophy. In ABD, serum BGP had the lowest average value, less than in patients with normal bone (NS). This finding is in accordance with the low level of ObS/BS. In addition ABD differed from OM in terms of alkaline phosphatase.

Discussion

The histopathology of renal osteodystrophy in patients with predialysis chronic renal failure is less known than in dialysis patients, mainly because of lack of skeletal symptoms in these patients and a less definite indication for a bone biopsy. Several studies have been published [2-6,17,18] and some of these reports have underlined the occurrence of hyperparathyroid changes and of mixed osteomalacia and hyperparathyroid bone disease [2,4]. Some reports are, in part, contradictory, especially with respect to the prevalence of osteomalacia [3,4]. Dahl et al. [3] have reported that OM is extremely rare in the predialysis stage, while Mora Palma et al. [4] found a high percentage of cases with osteomalacic alterations, mainly associated with chronic tubulointerstitial nephropathy and prevailing metabolic acidosis. Most reports on ABD deal with dialysis patients [19,20]. However, Cohen Solal et al. [18] recently reported on this type of renal osteodystrophy in predialysis stage as a consequence of treatment with calcidiol and consequent increase in calcitriol serum levels. Several other authors have reported on ABD in predialysis stage [5-7]. Hutchison et al. (5) and Hernandez et al. [6] published studies on series of ESRF patients, biopsied just before entering dialysis treatment. About 28 and 30%, respectively, of their patients were affected by ABD. In both series, patients with ABD had lower levels of intact PTH compared to the other groups. However the patients in both
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Table 2. Average (SD) of humoral and histomorphometric and histodynamic parameters in the histological classes

<table>
<thead>
<tr>
<th>parameter</th>
<th>ABD</th>
<th>MMO</th>
<th>OM</th>
<th>AMO</th>
<th>HP</th>
<th>ANOVA</th>
<th>N. values</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>10</td>
<td>9</td>
<td>26</td>
<td>7</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>M/F</td>
<td>6/4</td>
<td>4/5</td>
<td>15/11</td>
<td>4/3</td>
<td>14/8</td>
<td>1/1</td>
<td>-</td>
</tr>
<tr>
<td>Age (y)</td>
<td>51.2±11</td>
<td>33.7±12</td>
<td>46.1±15</td>
<td>53.9±9.4</td>
<td>53.8±11</td>
<td>21-45</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cr (mg/dl)</td>
<td>2.89±1.6</td>
<td>3.63±0.09</td>
<td>5.24±2.6</td>
<td>5.99±3.09</td>
<td>6.38±2.2</td>
<td>8.2-9.0</td>
<td>&lt;0.0008</td>
</tr>
<tr>
<td>Ccr (ml/min)</td>
<td>32.2±17.0</td>
<td>21.9±6.0</td>
<td>19.8±10.6</td>
<td>15.9±12.7</td>
<td>13.6±7.28</td>
<td>6.0-15.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ca (mg/dl)</td>
<td>9.37±0.57</td>
<td>9.13±0.32</td>
<td>9.21±0.74</td>
<td>8.21±1.49</td>
<td>8.56±0.98</td>
<td>9.1-9.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>P (mg/dl)</td>
<td>3.76±0.83</td>
<td>3.91±0.94</td>
<td>4.90±1.07</td>
<td>3.99±1.18</td>
<td>4.65±1.24</td>
<td>6.8-7.9</td>
<td>&lt;0.0006</td>
</tr>
<tr>
<td>AP (mU/ml)</td>
<td>84.2±32.5</td>
<td>72.4±36.2</td>
<td>99.3±47.6</td>
<td>181.4±57.2</td>
<td>137.8±99.9</td>
<td>78-225</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PTH (s-iter, mg/ml)</td>
<td>1.06±1.0</td>
<td>1.53±1.2</td>
<td>3.09±4.5</td>
<td>2.38±1.83</td>
<td>3.51±2.5</td>
<td>4.5-65</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PTH intact (pg/ml)</td>
<td>51.6±13.4</td>
<td>113.4±126</td>
<td>105.3±104</td>
<td>152.6±199</td>
<td>245.7±138</td>
<td>355-1440</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BGP (ng/ml)</td>
<td>16.4±11.4</td>
<td>13.2±5.2</td>
<td>26.1±18.4</td>
<td>52.8±66</td>
<td>46.3±38.8</td>
<td>30-112</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HCO3 (meq/l)</td>
<td>23.15±1.6</td>
<td>19.81±3.1</td>
<td>19.39±2.9</td>
<td>16.74±1.2</td>
<td>19.55±3.9</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>parameter</th>
<th>ABD</th>
<th>MMO</th>
<th>OM</th>
<th>AMO</th>
<th>HP</th>
<th>ANOVA</th>
<th>N. values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca (mmol/l)</td>
<td>2.07±0.53</td>
<td>2.07±0.53</td>
<td>2.07±0.53</td>
<td>2.07±0.53</td>
<td>2.07±0.53</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P (mmol/l)</td>
<td>1.07±0.53</td>
<td>1.07±0.53</td>
<td>1.07±0.53</td>
<td>1.07±0.53</td>
<td>1.07±0.53</td>
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<td>-</td>
</tr>
<tr>
<td>PTH (ng/ml)</td>
<td>25.0±11.4</td>
<td>25.0±11.4</td>
<td>25.0±11.4</td>
<td>25.0±11.4</td>
<td>25.0±11.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1,25 (OH) Vitamin D3 (ng/ml)</td>
<td>1.00±1.00</td>
<td>1.00±1.00</td>
<td>1.00±1.00</td>
<td>1.00±1.00</td>
<td>1.00±1.00</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

N, normal bone; ABD, adynamic bone disease; MMO, mild mixed osteodystrophy; OM, osteomalacia; AMO, advanced mixed osteodystrophy. ANOVA does not include HP.

Studies were on calcium carbonate for control of serum phosphate. Therefore the occurrence of a relatively high percentage of ABD in these series might not be correspondent to the natural prevalence of renal osteodystrophy in uraemic patients on conservative treatment and might probably be assigned to a relative suppression of PTH secretion due to calcium-containing phosphate binders, resulting in a more frequent emergence of the ABD pattern.

The study presented here is the only investigation on the prevalence of different categories of renal osteodystrophy, in a relatively large number of patients with varying degrees of renal failure. Although this study is cross-sectional in nature, based on a small number of patients for each histological class, and lacking some histodinematic data, it allows greater speculation on the natural evolution of renal osteodystrophy with increasing severity of chronic renal failure than previous reports [3-6]. The patients underwent a bone biopsy on a routine basis, a fact ruling out selection of patients, except for a definite preference for more advanced stages of renal failure. Therefore the sample should be considered representative of the population of predialysis renal failure. In addition, none of the patients was ever exposed to aluminium-containing phosphate binders, and histochemistry showed that no aluminium contamination was present in any case. The results of serum and bone aluminium in an appreciable section of this population under study has been already published and found to be slightly above normal values [21], and never in the 'toxic' range.

From several studies on the effect of aluminium on bone in dialysis patients, we have been accustomed to consider OM and ABD as two expressions of aluminium contamination. Moreover, the two conditions have very convincingly underlined the difference in aetiology of the two conditions and the autonomy of aluminium-related bone disease [22-24]. Several reports have very convincingly Underlined the difference in natural evolution of renal osteodystrophy with increasing severity of chronic renal failure than previous reports [3-6]

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Some interesting observations have been made in comparing normal bone patients with those affected by ABD. In ABD, serum iPTH ranges from normal to moderately elevated levels. However, on average, ABD patients show not lower, but higher levels of PTH compared to patients with normal bone. This is despite a lower rate of histologically proven bone turnover and an evident paucity of osteoblastic cells, as shown by a significantly lower ObS/BS%, a fact which is in line with the finding of a lower serum level of osteocalcin. Therefore, as has already been reported for ABD in dialysis patients, intact PTH serum levels may also not be a good marker of bone turnover in need of replacement [25]. This finding also suggests, as already proposed by others for dialysis patients [20,25], that ABD is found when resistance of bone to PTH is established as a consequence of renal failure, and when the increase of PTH is not sufficient to overcome the acquired resistance of bone tissue. From the apparently progressive nature of the different forms of bone disease it might be hypothesized that these lesions represent an evolution from normal bone and ABD to pure hyperparathyroid bone disease or associated osteomalacic lesions as serum PTH levels rise.

Other publications [5,6] have reported the occurrence of ABD also in very advanced predialysis renal failure, a fact which could be considered in contrast with our findings. In the study of Hutchison et al. [5], patients with ABD had the lowest values of intact PTH, much lower than in the few cases with osteomalacia. Therefore treatment with calcium carbonate was probably able to keep serum PTH at relatively low levels. Also in the study of Hernandez et al. [6], serum intact PTH in ABD patients was 3–4 times the upper level of normal values; however, it was definitely lower than in other types of renal bone disease. Therefore, one might postulate that ABD can appear any time once the levels of PTH are decreased by treatment with calcium carbonate or vitamin D analogues and metabolites [18,26], or due to the presence of diabetes [27]. The underlying resistance of bone to PTH would in this case become evident. From our results it can be stated that relative bone resistance to PTH plays a common role in the pathogenesis of ABD in predialysis and dialysis patients. Resistance of bone to PTH has been reported in former studies [28].

Recently, this concept has been re-evaluated by many authors, with special regard to ABD [20,25,29]. As for the causes of this resistance, there is no uniform interpretation [30]. Resistance of bone and other tissues to PTH has been linked to downregulation of PTH receptors similar to findings regarding the kidney and the liver [31]. In chronic renal failure, the PTH–PTHrP receptor mRNA is also downregulated; a phenomenon apparently reversed by verapamil treatment [32]. Similar mechanisms could be operative in osteoblastic cells.
More definitive information on the evolution of histological patterns in predialysis chronic renal failure will be possible through longitudinal studies. A practical consideration derives from our results. Namely too early and aggressive treatment of initial hyperparathyroidism should be avoided and tolerance to a mild elevation of serum iPTH levels should be practiced.

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References


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