Trends in renal osteodystrophy: a survey from 1983 to 1995 in a total of 2248 patients

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Key words: adynamic uraemic osteodystrophy; aluminium; hyperparathyroidism; metabolic bone disease; mineralized bone histology; renal osteodystrophy

Introduction

The renal bone disease developing in patients with end-stage renal failure, i.e. renal osteodystrophy, is not a uniform metabolic bone disease [1-5]. Classically, the various forms of renal osteodystrophy encompass predominant hyperparathyroid bone disease (osteoitis fibrosa), mixed uraemic osteodystrophy, and low turnover uraemic osteodystrophy (osteomalacia and adynamic bone disease) [1-5]. In the 1970s, the heterogeneity in bone lesions was attributed, at least in part, to co-existence of aluminium toxicity in bone [1,6-9]. Control of aluminium content in dialysate and replacement of aluminium-containing phosphate binders with calcium salts have resulted in a progressive and definite decrease in aluminium-related bone disease [9-11]. Moreover, changes in the management of dialysed patients have been made during the last 10 years.

The present study was undertaken: (i) to investigate the evolution of renal osteodystrophy during the last 13 years in relation with patients' characteristics and treatment modalities; and (ii) to attempt to identify factors that could be associated with the pattern of renal osteodystrophy.

Subjects and methods

Patient population

Patients with end-stage renal failure on chronic maintenance dialysis who underwent bone biopsies during the last 13 years (from January 1983 till October 1995) were reviewed. The inclusion criteria were 18 years of age and older; bone samples of adequate size and quality; tetracycline labelling; and sufficient information regarding mode of dialysis, duration of dialysis, knowledge of pre-existing parathyroidectomy, vitamin D or desferroxamine therapy, and prescription of phosphate binders. The exclusion criterion was failed transplant within the last 6 months.

Methods

Twenty days prior to bone biopsy, all patients began receiving tetracycline hydrochloride for bone labelling at a dose of 500 mg p.o. b.i.d. for 2 days. No tetracycline antibiotic was administered for the following 10-14 days. Tetracycline hydrochloride or demeclocycline hydrochloride (Declomycin®, Lederle, Wayne, NJ) was administered for the next 4 days at 500 or 300 mg p.o. b.i.d., respectively. Phosphate binders and other antacids were not given on days of tetracycline administration. All patients were biopsied 3-4 days after receiving the second tetracycline label.

Bone samples were taken from the anterior iliac crest either with an electric drill (Straumann AG, Waldenburg, Switzerland) [12] or with a transiliac manual trocar under local or short-term general anaesthesia.

Bone samples were fixed in absolute ethanol, dehydrated and embedded in methylmethacrylate as previously described [1]. Serial sections 3 and 7 µm thick were cut with a Reichert-Jung microtome, Model 1140 (Reichert-Jung, Buffalo, NY). Sections 3 µm thick were stained with the modified Goldner trichrome stain [13]. Serial sections 7 µm thick and unstained were prepared for phase contrast and fluorescent light microscopy. In addition, serial 7 µm sections were stained with the aurin tricarboxylic acid stain [14] and solochrome azurine [15] for detection of aluminium.

After microscopical analysis of the bone samples, patients were classified into one of the following four categories.

1. Predominant hyperparathyroid bone disease (PHBD). The main abnormality is represented by a marked increase in bone turnover associated with an increased number of osteoblasts and osteoclasts, abundance of woven osteoid, and pronounced peritrabecular and marrow fibrosis. The fraction of trabecular surface exhibiting tetracycline labelling is high. Mineral apposition rate in lamellar bone is normal or increased. In woven bone, diffuse or irregular uptake of tetracycline represents a prominent feature.

2. Mixed uraemic osteodystrophy (MUO). This form is characterized by signs of secondary hyperparathyroidism and...
local decrease in bone remodelling and/or defective mineralization. Active foci with numerous osteoblasts, woven osteoid, peritrabecular fibrosis and increased tetracycline uptake co-exist with adjacent lamellar sites with lower cellularity and tetracycline uptake. The ratio between high and low turnover remodelling sites may vary from patient to patient. The number of osteoclasts is usually increased.

(3) Adynamic bone disease (ABD), characterized by dramatically reduced bone turnover with a paucity of osteoid and bone cells, and a marked decrease in active remodelling sites and tetracycline uptake.

(4) Low turnover osteomalacia (LTOM) typified by a profound decrease in bone turnover associated with a marked increase in osteoid volume and surface and wide osteoid seams. The number of active remodelling sites is dramatically reduced and mineralization is severely reduced or virtually absent.

Bone biopsies were independently interpreted by the two authors; when discrepancies occurred in borderline cases (less than 1%), additional sections were cut. The slides were reviewed, discussed and assigned to one of the four categories.

The extent of aluminium deposits at the osteoid–bone interface was measured (Osteoplan II System, Kontron, Munich, Germany). Aluminium deposition in bone was considered positive when the aluminium deposits were greater than or equal to 30% of the trabecular surface.

The laboratory database was built in Data Entry (SPSS, Inc, Chicago, IL) and analysed using SPSS software package for Windows (SPSS, Chicago, IL) employing an IBM PS2 computer (IBM Corp; Boca Raton, FL). Non-numerical data were coded when appropriate. All coding and entries were double checked, and randomly selected cases were verified monthly.

Differences in continuous variables over the years were assessed by standard analysis of variance. Differences in distribution were analysed using the chi-square test. Discriminant, univariate, multivariate and logistic regression analyses were performed to distinguish factors associated with ABD.

Results

Patient characteristics

Among the 2298 patients screened, 2248 fulfilled the selection criteria. Patients lived in various geographic areas of the USA (26 states) and were dialysed using usual and customary dialytic procedures in 138 different dialysis units.

There were 1144 women (50.9%) and 1104 men (49.1%). The ratio of men to women did not change over the last 13 years (Table 1). Also, women were significantly older than men, a trend observed in all but one year (1990) from 1983 to 1995 (Table 1). There was a trend towards an increase in age of patients at time of bone biopsy from 1983 to 1993, which was no longer observed thereafter (Table 1).

One thousand eight hundred and thirty patients (81.4%) were on chronic maintenance haemodialysis (HD), and 418 (18.6%) were on continuous ambulatory peritoneal dialysis (CAPD). The proportion of patients on HD or CAPD did not change over time (Table 1). Patients undergoing HD or CAPD started dialysis at the same age (47.5 ± 0.4 vs 46.0 ± 0.8 years, respectively). However, patients on CAPD were biopsied earlier after onset of dialysis than patients on HD (Table 1). This was observed every year since 1983 (Table 1).

The underlying kidney diseases were diabetes mellitus (14.9%), chronic glomerulonephritis (21%), hypertensive nephropathy (29.8%), polycystic kidney disease (12.7%), urolithiasis causes (4.9%), lupus (1.4%), Goodpasture’s syndrome (1.2%), and other rare diseases of unknown origin (14.1%). Over the years the only noticeable change was represented by a significant relative increase in the number of patients with diabetic nephropathy (Table 2). The percentage of women was greater among the diabetic than non-diabetic patients (59 vs 41%, P < 0.01) but this was not a constant observation during the 13 years of the survey. Diabetic patients started dialysis later than non-diabetic patients, but they had a diagnostic bone biopsy approximately 2 years earlier than the other patients after initiation of dialysis (Table 2). However, diabetics were as old as the non-diabetics at time of biopsy (54 ± 0.7 vs 52 ± 0.4 years). In this survey, the percentages of diabetic and non-diabetic patients dialysed by CAPD (15.3 vs 15.3%) and HD were not different.

Treatment prior to bone biopsies

The number of patients taking aluminium-containing phosphate binders increased significantly from 1983 to 1987 and decreased thereafter (Table 3). It is of note that in 1995, approximately 1 of 5 patients were still taking aluminium salts for phosphate binding. Of those, 61.3% take aluminium hydroxide alone and 38.7% in association with calcium carbonate (Table 3). There was a significant increase in the number of patients taking calcium salts during the 13 years of the

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Table 1. Clinical characteristics of 2248 patients who underwent a diagnostic bone biopsy from 1983 to 1995

<table>
<thead>
<tr>
<th>Year</th>
<th>Men (%)</th>
<th>Age (years)</th>
<th>CAPD (%)</th>
<th>Duration on dialysis (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Women</td>
<td>Men</td>
<td></td>
<td>CAPD HD</td>
</tr>
<tr>
<td>1983</td>
<td>49.3</td>
<td>51 ± 2.4</td>
<td>44 ± 2.5</td>
<td>23.8</td>
</tr>
<tr>
<td>1984</td>
<td>52.9</td>
<td>51 ± 1.9</td>
<td>48 ± 1.7</td>
<td>19.8</td>
</tr>
<tr>
<td>1985</td>
<td>49.7</td>
<td>54 ± 1.5</td>
<td>51 ± 1.6</td>
<td>17.9</td>
</tr>
<tr>
<td>1986</td>
<td>50.7</td>
<td>55 ± 1.3</td>
<td>49 ± 1.5</td>
<td>15.0</td>
</tr>
<tr>
<td>1987</td>
<td>46.7</td>
<td>56 ± 1.3</td>
<td>51 ± 1.4</td>
<td>14.8</td>
</tr>
<tr>
<td>1988</td>
<td>52.2</td>
<td>56 ± 1.3</td>
<td>51 ± 1.4</td>
<td>24.5</td>
</tr>
<tr>
<td>1989</td>
<td>51.5</td>
<td>54 ± 1.7</td>
<td>53 ± 1.7</td>
<td>12.2</td>
</tr>
<tr>
<td>1990</td>
<td>47.6</td>
<td>53 ± 1.5</td>
<td>53 ± 1.5</td>
<td>20.2</td>
</tr>
<tr>
<td>1991</td>
<td>48.1</td>
<td>53 ± 1.6</td>
<td>51 ± 1.6</td>
<td>17.4</td>
</tr>
<tr>
<td>1992</td>
<td>45.6</td>
<td>55 ± 1.2</td>
<td>50 ± 1.4</td>
<td>14.6</td>
</tr>
<tr>
<td>1993</td>
<td>46.5</td>
<td>56 ± 1.5</td>
<td>52 ± 1.8</td>
<td>25.6</td>
</tr>
<tr>
<td>1994</td>
<td>50.0</td>
<td>52 ± 1.8</td>
<td>49 ± 1.8</td>
<td>23.4</td>
</tr>
<tr>
<td>1995</td>
<td>50.5</td>
<td>48 ± 2.6</td>
<td>45 ± 2.1</td>
<td>23.6</td>
</tr>
</tbody>
</table>

*Different from women, P < 0.01.
*Different from patients on CAPD, P > 0.01.
Table 2. Clinical characteristics of diabetic and non-diabetic patients

<table>
<thead>
<tr>
<th>Year</th>
<th>Diabetics (%</th>
<th>Age at onset of dialysis (years)</th>
<th>Duration on dialysis (years)</th>
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<tr>
<td></td>
<td></td>
<td>Diabetics</td>
<td>Non-diabetics</td>
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<tr>
<td>1983</td>
<td>13.7</td>
<td>46.6±4.7</td>
<td>4.01±2.0</td>
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<td>1984</td>
<td>15.8</td>
<td>44.0±4.9</td>
<td>46.6±1.6</td>
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<tr>
<td>1985</td>
<td>12.5</td>
<td>50.9±3.9</td>
<td>45.9±1.4</td>
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<tr>
<td>1986</td>
<td>16.2</td>
<td>45.0±3.8</td>
<td>46.4±1.5</td>
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<tr>
<td>1987</td>
<td>9.9</td>
<td>53.5±2.0</td>
<td>48.8±1.4</td>
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<tr>
<td>1988</td>
<td>20.5</td>
<td>57.8±3.1</td>
<td>48.0±1.4</td>
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<td>1989</td>
<td>12.4</td>
<td>50.2±2.8</td>
<td>46.0±1.6</td>
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<tr>
<td>1990</td>
<td>17.3</td>
<td>51.4±2.9</td>
<td>47.6±1.3</td>
</tr>
<tr>
<td>1991</td>
<td>12.3</td>
<td>46.3±2.6</td>
<td>46.3±1.6</td>
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<tr>
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<td>12.6</td>
<td>53.3±2.0</td>
<td>48.0±1.3</td>
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<tr>
<td>1993</td>
<td>8.7</td>
<td>52.4±1.9</td>
<td>47.5±1.9</td>
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<tr>
<td>1994</td>
<td>20.6</td>
<td>47.5±2.5</td>
<td>44.5±1.9</td>
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<tr>
<td>1995</td>
<td>16.3*</td>
<td>52.6±3.9</td>
<td>39.4±2.2</td>
</tr>
<tr>
<td>Total</td>
<td>13.9</td>
<td>51.1±0.8</td>
<td>46.9±0.4</td>
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</table>

*Significant increase with time, P<0.05.
*Significant change with time, P<0.01.

Table 3. Treatment regimens prior to bone biopsies in 2248 dialysis patients

<table>
<thead>
<tr>
<th>Year</th>
<th>Al binders (% patients)</th>
<th>Calcium salts (% patients)</th>
<th>Deferoxamine treatment (% patients)</th>
<th>Post-parathyroidectomy (% patients)</th>
<th>PO calcitriol treatment (% patients)</th>
<th>IV calcium treatment (% patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>20.9</td>
<td>19.4</td>
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<td>28.3</td>
<td>12.5</td>
<td>5.8</td>
<td>6.7</td>
<td>13.3</td>
<td>0</td>
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<tr>
<td>1985</td>
<td>42.6</td>
<td>21.7</td>
<td>7.4</td>
<td>5.3</td>
<td>18.0</td>
<td>0.5</td>
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<tr>
<td>1986</td>
<td>60.1</td>
<td>27.6</td>
<td>10.0</td>
<td>2.8</td>
<td>23.4</td>
<td>0</td>
</tr>
<tr>
<td>1987</td>
<td>72.5</td>
<td>39.5</td>
<td>20.3</td>
<td>6.8</td>
<td>33.3</td>
<td>6.9</td>
</tr>
<tr>
<td>1988</td>
<td>46.6</td>
<td>41.5</td>
<td>20.1</td>
<td>3.4</td>
<td>29.0</td>
<td>2.8</td>
</tr>
<tr>
<td>1989</td>
<td>45.3</td>
<td>34.2</td>
<td>16.8</td>
<td>11.2</td>
<td>19.9</td>
<td>5.6</td>
</tr>
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<td>40.7</td>
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<td>3.2</td>
<td>11.6</td>
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<td>51.4</td>
<td>56.3</td>
<td>21.3</td>
<td>6.6</td>
<td>18.0</td>
<td>10.9</td>
</tr>
<tr>
<td>1992</td>
<td>49.3</td>
<td>62.2</td>
<td>16.5</td>
<td>4.2</td>
<td>18.9</td>
<td>16.5</td>
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<td>68.6</td>
<td>9.8</td>
<td>3.3</td>
<td>13.4</td>
<td>23.0</td>
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<tr>
<td>1994</td>
<td>20.4</td>
<td>75.9</td>
<td>11.2</td>
<td>1.9</td>
<td>6.5</td>
<td>24.1</td>
</tr>
<tr>
<td>1995</td>
<td>20.2*</td>
<td>79.8*</td>
<td>4.6*</td>
<td>0</td>
<td>10.5</td>
<td>24.1*</td>
</tr>
<tr>
<td>Total</td>
<td>42.6</td>
<td>46.4</td>
<td>13.4</td>
<td>4.7</td>
<td>19.0</td>
<td>9.0</td>
</tr>
</tbody>
</table>

*Significant changes with time, P<0.01.

Reasons for performance of bone biopsies

(1) Bone symptoms such as fractures and/or bone pain were found in 18.1% of the patients (Table 4) with a slight recent trend towards a further increase (Table 4). Among patients with bone pain, 26.7% experienced at least one fracture (Table 4); these were 4.8% of the total number of patients studied over the 13 years of the survey. Patients with bone symptoms were on dialysis longer than asymptomatic patients (5.4±0.2 vs 4.8±0.1 years, P<0.001) and only 9.9% of them were hypercalcaemic at the time of bone biopsy. There were no other differences, including biochemical or histological profiles or treatment modalities, between symptomatic and asymptomatic patients.

(2) Hypercalcaemia was the major reason for the performance of bone biopsies in 13.9% of the patients.
These patients had been treated with or without calcitriol (32.4% and 67.6%, respectively; Table 4). The percentage of bone biopsies performed for hypercalcaemia did not change with time (Table 4). Comparison between hypercalcaemic and normocalcaemic patients showed that hypercalcaemic patients were more likely to have histological signs of ABD (23.8 vs 13.9%, \( P < 0.01 \)) and bone aluminium accumulation (69.4 vs 52.3%, \( P < 0.01 \)).

(3) Extraosseous calcifications were found in 34 patients (1.5%). Only 12.5% of these patients also presented with hypercalcaemia. No significant factor could be associated with extraosseous calcifications, except ectopic calcifications, which occurred more often in male than in female patients (73 vs 27%, \( P < 0.05 \)).

(4) Suspcion of aluminium-related bone disease based on high serum aluminium concentrations or positive deferoxamine test or signs of dementia were the reasons for biopsy in 716 patients (31.9%). Stainable aluminium was found in two-thirds of the patients biopsied for this purpose (66.9%) but also in 54.6% of patients biopsied for other reasons. Bone biopsies to rule out aluminium-related bone disease increased over the years, plateaued in the late 1980s and early 1990s and decreased thereafter (Table 4). However, in 1995, 38% of biopsies were still done to determine bone aluminium accumulation (Table 4), and this diagnosis was confirmed in 55.8% of them.

(5) Elevated serum parathyroid hormone (PTH) was the reason for bone biopsies in 535 patients (23.8%). Bone biopsies were also done prior to parathyroidectomy in 206 patients (9.2%). There were no significant changes in indication for biopsy secondary to elevated serum PTH, while there was an increase in bone biopsies performed prior to parathyroidectomy from the late 1980s until recently (Table 4). Bone histology of patients biopsied because of elevated serum PTH showed all forms of renal osteodystrophy: PHBD (24%), MUO (57%), LTOM (5.6%) and ABD (13.4%). Prior to parathyroidectomy, bone biopsies confirmed PHBD in 43.2% of the patients only and showed MUO in 48.1%, LTOM in 1.9% and adynamic uraemic bone disease in 6.8% of the patients.

(6) Various other causes such as hypocalcaemia, suspicion of oxalosis, weakness and anaemia were reasons for bone biopsies in 38 patients (1.6%).

**Biochemical and hormonal profiles**

Serum biochemical measurements of calcium, phosphorus and alkaline phosphatase did not show a trend towards change over the years. Methods of measuring serum PTH varied greatly from one centre to another and with time. The trend to measure intact PTH is relatively recent, and the number of PTH levels measured with this RIA was available in 410 patients since 1992.

Serum calcium was significantly greater in patients with ABD without aluminium accumulation than in those with ABD and with aluminium accumulation or any other histological forms of renal osteodystrophy (Table 5). Serum phosphorus was lower in patients with LTOM without aluminium accumulation than in the other groups (Table 5). Serum alkaline phosphatase was significantly greater in patients with PHBD and LTOM than in patients with MUO or ABD regardless of bone aluminium accumulation (Table 5). Serum PTH was greater in patients with PHBD than in those with MUO and ABD or LTOM (Table 5).

**Bone histology**

The overall distribution of the four histological forms of renal osteodystrophy was as follows: PHBD, 24.5%; MUO, 52.9%; LTOM, 6.2%; and ABD, 16.4%. Over the 13 years of the survey, however, this distribution varied (Figure 1). MUO was found in the majority of patients over the years, however a slight decrease in...
Table 5. Serum biochemical and hormonal parameters of bone according to histological forms of renal osteodystrophy

<table>
<thead>
<tr>
<th></th>
<th>Adynamic bone disease</th>
<th>Low turnover osteomalacia</th>
<th>Mixed uraemic osteodystrophy</th>
<th>Hyperparathyroid bone disease</th>
<th>Normal values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBA &lt; 30%</td>
<td>SBA &gt; 30%</td>
<td>SBA &lt; 30%</td>
<td>SBA &gt; 30%</td>
<td></td>
</tr>
<tr>
<td>Serum calcium (mg/dl)</td>
<td>11.4 ± 1.5 *</td>
<td>9.9 ± 0.1</td>
<td>9.1 ± 0.2</td>
<td>9.9 ± 0.1</td>
<td>8.4 – 10.2</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dl)</td>
<td>6.1 ± 0.2</td>
<td>6.9 ± 0.5</td>
<td>4.5 ± 0.2</td>
<td>6.9 ± 1.2</td>
<td>7.2 ± 0.3</td>
</tr>
<tr>
<td>Alkaline phosphatase (IU/L)</td>
<td>97.9 ± 8.5</td>
<td>118 ± 8.0</td>
<td>193 ± 52.6</td>
<td>223 ± 22.4 *</td>
<td>380 ± 43.3 b</td>
</tr>
<tr>
<td>Intact PTH (pg/ml)</td>
<td>406 ± 233</td>
<td>312 ± 226</td>
<td>i.n.</td>
<td>i.n.</td>
<td>774 ± 269 *</td>
</tr>
</tbody>
</table>

i.n., insufficient number; SBA, stable bone aluminium.
*Different from other histological forms.
*bDifferent from patients with adynamic bone disease or mixed uraemic osteodystrophy.

Overall, 58.5% of the patients exhibited positive stainable aluminium at >30% of the trabecular surface. There were more patients with this diagnosis in the PHBD group (Figure 4), and this did not change with time. The proportion of patients with stainable aluminium at >30% of the trabecular surface was approximately 50% in 1984 and remained stable until 1992, when it decreased to approximately 40%. In 1985, approximately 80% of the patients with PHBD showed aluminium accumulation (Figure 3). However, in 1995, aluminium deposition was observed in all patients with PHBD, with low bone turnover. In patients presenting with low bone turnover, either osteomalacia or ABD, the number of patients with aluminium deposition in bone increased from 1983 to 1995 (Figure 3). However, in 1995, only 20% of the patients with low bone turnover showed aluminium deposition. In patients with PHBD, the proportion of patients with aluminium accumulation increased from 1983 to 1995 (Figure 4), and this did not change with time.

In a large number of patients with this diagnosis, the number of patients with aluminium deposition increased until 1984, and the number of patients with this histological bone disease increased until the late 1980s (Figure 1). The incidence of LTOM decreased progressively during the last 13 years. The number of patients with LTOM decreased constantly until 1985, but increased gradually thereafter (Figure 1). ABD was first seen in 1984, and the number of patients with this histological bone disease increased until 1988 but then remained stable (Figure 1). Thereafter, there were more patients with stainable aluminium >30% in the LTOM, ABD and MUO groups than in the PHBD group (Figure 5). From 1984 to 1995, the proportion of patients with bone aluminium accumulation in the PHBD group (Figure 4) and this did not change with time. There were more patients with aluminium accumulation in the PHBD group (Figure 4), and this did not change with time. There were more patients with aluminium accumulation in the PHBD group (Figure 4), and this did not change with time.

Bone aluminium accumulation

% Patients/yr
Fig. 2. (A) Evolution of the number of patients with adynamic bone disease on CAPD (---) and HD (—O—) from 1983 to 1995. (B) Evolution of the number of patients with predominant hyperparathyroidism on CAPD (---) and HD (—O—) from 1983 to 1995.

Fig. 3. Evolution of the proportion of patients with (---) and without (—O—) stainable aluminium >30% of bone surface from 1983 to 1995.

Fig. 4. Mean value of aluminium surface/bone surface in patients exhibiting stainable aluminium >30% of bone surface with predominant hyperparathyroidism (PHPT), mixed uraemic osteodystrophy (MUO), low turnover osteomalacia (LTOM) and adynamic bone disease (ABD).

Fig. 5. Percentage of patients with predominant hyperparathyroidism (PHPT), mixed uraemic osteodystrophy (MUO), low turnover osteomalacia (LTOM) and adynamic bone disease (ABD) with (□) or without (○) stainable aluminum >30% of bone surface.

Fig. 6. Percentage of patients with bone aluminium accumulation in 1984 (□) and 1995 (○).
Factors associated with the various histological entities

Aluminium-related bone disease. Patients with stainable bone aluminium at >30% of the trabecular surface were older, started dialysis at an older age, and had longer duration on dialysis at time of biopsy than patients with stainable aluminium at <30% of the trabecular surface (Table 6). Also, patients on HD and those taking aluminium hydroxide were more prone to develop aluminium accumulation than patients on CAPD and patients not taking aluminium salts at time of biopsy (Table 6). Logistic regression analysis did not reveal any other useful characteristics for prediction of bone aluminium accumulation, including serum PTH and therapy with deferoxamine.

Adynamic bone disease. Factors associated with ABD, with or without aluminium accumulation, include CAPD, diabetes, older age of patients at the onset of dialysis and at time of biopsy, and shorter duration on dialysis (Table 7). When patients without aluminium accumulation were analysed separately, the relationship between these factors and ABD was even more pronounced. In addition, intake of calcium salts was found to be associated with the diagnosis of ABD in patients without aluminium accumulation (Table 7). Diabetic patients on CAPD showed the higher proportion of ABD regardless of presence or absence of aluminium accumulation (Figure 7).

Predominant hyperparathyroidism. Patients with PHBD presented opposite characteristics to those of patients with ABD. They were younger when dialysis was instituted and at time of biopsy but had undergone dialysis treatment for a longer period of time and were more likely to be non-diabetic and to be dialysed by HD (Table 7). Also, it is of note that intravenous calcitriol was prescribed significantly more often in patients with PHBD than in patients with ABD (Table 7).

### Discussion

Thirteen years ago, most patients on dialysis presented with secondary hyperparathyroidism alone (PHBD) or associated with various degrees of mineralization defect (MUO). The 1980s were marked by an increase of aluminium-related bone disease. While aluminium intoxication was prevailing, fewer dialysed patients presented with PHBD as a result of the direct action of aluminium on parathyroid gland activity [16,17], its inhibitory effect on bone cell recruitment, bone cell activity and bone mineralization [18–20]. During that time approximately half of the patients exhibited MUO while the most severe cases of aluminium-related bone disease were associated with LTOM or a new histological form, ABD. The latter entity increased during the subsequent years and became a common feature of renal osteodystrophy [9–11,21,22]. It was initially thought to be strongly related to aluminium intoxication.

With the avoidance of dialysate contamination by aluminium, replacement of aluminium hydroxide by calcium salts [23,24], and the therapeutic removal of aluminium from bone and other organs by deferoxamine [25], aluminium-related disease was doomed to disappear. However, this has not yet been fully accomplished. Approximately 10 years elapsed between the time dialysed patients could benefit from an aluminium-free regimen and a substantial decrease in aluminium-related bone disease. This is due in part to: (i) the previous long-standing cumulative intake of aluminium-containing phosphate binders by patients already...
on dialysis at the time preventive measures were implemented; and/or (ii) the lack of FDA approval of deferoxamine as an aluminium chelator and hence the reluctance of some nephrologists to use deferoxamine treatment particularly since rare but serious potential side effects were described [26–29]. Also, accidental contamination of dialysate and intake of over-the-counter medications containing aluminium may be responsible for bone aluminium accumulation in some newly dialysed patients. Most importantly, in some patients control of phosphate cannot be achieved solely by calcium salts, and aluminium hydroxide needs to be added for phosphorus control. Indeed, in 1995, 20% of patients still received aluminium-containing phosphate binders. This indicates that, despite the real decrease in aluminium intoxication, nephrologists still need to be vigilant. It is probable that aluminium bone disease will never completely disappear until better means of phosphate binding are found. Currently only one-fourth of dialysis patients present with bone aluminium accumulation.

The two-thirds decrease in prevalence of bone aluminium accumulation since the late 1980s has resulted in a change in the pattern of renal osteodystrophy. With less aluminium intoxication, patients on chronic maintenance dialysis are expected to exhibit more signs of secondary hyperparathyroidism [18,30]. Indeed, the present study showed that the number of patients with PHBD steadily increased since 1990 in both HD and CAPD patients. On the other end of the spectrum, the number of patients with LTOM decreased, while there is no apparent change in the number of patients with ABD. However, ABD is now more frequently detected in the absence of aluminium accumulation [9–11,21,22].

Recent evidence shows that ABD is not only a histological entity but has clinical relevance. Patients with this abnormality were found to have abnormal calcium homeostasis [31] and higher morbidity and mortality rates than patients exhibiting other histological abnormalities [22]. In the present cross-sectional study, ABD was not significantly associated with more bone pain or fractures than the other forms of renal osteodystrophy. The current study shows that the percentage of patients with ABD is approximately 20%, which is close to the percentage found in our previous extensive survey from several geographical areas [9]. This finding differs from other reports that found 40% of patients (mainly on CAPD) from the same geographical area with ABD [11,21,22]. In those studies, most bone biopsies were performed for research purposes. It is unlikely that the difference in prevalence of ABD between the present and previous studies is due to a selection processes. In the studies conducted in Canada the addition of patients referred for clinical findings suggestive of bone disease to randomly selected patients from the same geographical area did not alter the distribution of the various histological lesions [9]. This is in agreement with our recent study which showed that patients biopsied for diagnostic purpose are representative of the population of patients on dialysis selected at random [32].

In the present study, there was no geographical difference in the prevalence of the various histological forms of renal osteodystrophy. Therefore, the prevalence of more diabetic patients on CAPD in the Canadian studies may account for the large number of patients with ABD. Indeed, ABD was also seen in approximately 40% of the diabetic patients on CAPD included in our present study.

Our data show that nephrologists today are confronted with dialysed patients who have either PHBD with various degrees of a mineralization defect, just as they did during the 1970s, or ABD. To date, rational preventive and therapeutic strategies have been adopted to prevent or suppress secondary hyperparathyroidism by control of serum calcium and phosphorus, together with supplementation of the missing hormone, calcitriol [33–36]. The present study demonstrates the increased use of calcium salts and calcitriol therapy, especially IV, during the past few years. The impact of these new therapeutic strategies is difficult to determine based on data of the present study since the widespread implementation of these therapeutic modalities co-exists with the decline in aluminium intoxication. However, it appears that widespread administration of calcium salts, together with more diabetic patients entering dialysis, especially CAPD, may represent a strong predisposition for the development of ABD. Also, treatment with calcitriol together with less aluminium may have contributed to the recent, though moderate, decrease in the number of patients with MUO.

The increase in the number of patients with PHBD despite IV calcitriol treatment is puzzling. With the widespread use of calcium salts and calcitriol therapy, it has become necessary to decrease dialysate calcium content to 2.5 mEq/l or less to avoid hypercalcaemia. It is conceivable that this exposure to low dialysate calcium more than offsets the effects of therapeutic measures aimed at decreasing parathyroid gland overactivity. More studies are needed to address this important issue.

Another unanswered question is related to the optimal level of PTH maintenance of normal bone turnover. In a recent study, our laboratory found that serum iPTH concentrations between 65 and 450 pg/ml, seen in the majority of dialysis patients, are unpredictable of bone turnover. In these patients, bone histology may show either ABD, suggestive resistance of bone to PTH, or secondary hyperparathyroidism with various degrees of mineralization defect despite calcitriol therapy. This points to resistance of bone to calcitriol.

The concept of resistance of the skeleton to these two calcitropic hormones in chronic renal failure is not new [37–40]. As Hruska and Teitelbaum have pointed out [5], factors other than PTH and calcitriol may be involved in the regulation of bone turnover in dialysed patients and new pathophysiological avenues must be investigated. In particular, the disturbance in the expression of receptors for PTH and calcitriol in bone of dialysed patients has not been studied and
experimental data are conflicting [41–45]. Also, the participation of cytokines and growth factors, known to be abnormal in uraemia [46–57], deserves further study.

Research into these new areas may further improve the understanding of the pathophysiology of renal osteodystrophy and may serve as the basis for developing new preventative and therapeutic strategies that could improve the quality of life of patients on chronic maintenance dialysis. This becomes imperative since, despite recent efforts to alleviate the long-term effects of chronic renal failure on bone, the percentage of dialysed patients suffering from bone pain and fractures did not change during the 13 years of the present study.

Acknowledgements. We thank Richard M. Wheaton for his technical assistance in the preparation of bone slides, Mr Jamie Cohlmeyer for his help in data entry and Ms Louise Tipton for valuable secretarial assistance. This work was supported in part by grants from Dialysis Clinics, Inc. (L-105, L-106) and the National Kidney Foundation of Kentucky.

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