Dialysis Bone Disease

E RITZ, B KREMPIEN, G RIEDASCH, H KUHN, W HACKENG, F HEUCK
Medizinische Klinik Heidelberg; Pathologisches Institut Heidelberg; Katharinenhospital Stuttgart, German Federal Republic; Bergwegziekenhuis, Rotterdam, Holland

Uraemic osteodystrophy continues to be one of the major unsolved problems of regular haemodialysis. In the following the data derived from a survey of 282 patients (average duration of dialysis $16.7 \pm 12.3$ months) in 17 German haemodialysis centres are reported (Ritz et al, 1971a).

CLINICAL SYMPTOMS

One hundred and thirty-one individuals among the 282 patients examined (46%) presented at least one, and 46 patients (36% of the symptomatic individuals) more than one of the following symptoms:
- bone pain – 19.5% – of all patients,
- spontaneous fractures – 1%,
- loss of height – 1%,
- history of pseudogout – 19%,
- nonvascular extraosseous calcification – 19.5%,
- red eye syndrome – 12%,
- corneal calcification – 42%.

Parathyroidectomy has been performed in 15 (5.3%) of the 282 patients.

Signs and symptoms of uraemic bone disease are thus not uncommon; disabling symptoms are, however, distinctly rare.

The incidence of corneal calcification was so high that it was of no value in predicting bone disease.

X-RAY FINDINGS

Positive X-ray signs were found in 54% of all X-rays studied by a single examiner (Ritz et al, 1971b). A ground glass appearance of the skull was encountered in 32%, acroosteolysis of the lateral clavicle with enlargement of the acromioclavicular articulation in 18%, spongiosis of the compacta of the middle phalanges of the hand (ie splintering of the compacta and endosteal erosion from within) in 54%, spotty rarification of the spongiosa of the
phalanges in 28%, subperiosteal resorption of the radial aspect of the middle phalanges in 16%, irregular widening of the sacroiliac articulation in 4%, irregular widening of the symphysis in 6%, and the rugger jersey sign of the vertebrae in 7%. Bone cysts, periosteal new bone formation, subperiosteal resorption zones in the head of the tibia etc were seen only in individual patients.

All the signs mentioned are indicative of clinical osteitis fibrosa; Looser's zones, pointing to osteomalacia, were found in less than 1%.

Vascular calcification of the small arteries of the hand were observed in 6.9%, calcification of the iliac arteries in 28%. Nonvascular extrasosseous calcification occurred in 19%. These figures differ in some respects from preliminary data given elsewhere (Ritz et al, 1971c).

The incidence of positive X-ray signs tended to increase with increasing length of dialysis (eg ground glass appearance of the skull: 1 year 23%, 1 - 3 years 42.8%, 3 years 60%). The mineral content of the calcaneus, measured with the densitometric procedure after Heuck (1970) was markedly decreased (dialysis patients 148.7 ± 40.9 mg hydroxyapatite/ml bone volume (range 70 mg - 275 mg); controls (3rd decade): 246.2 ± 61.1). The cortical index of the second metacarpal after Barnett and Nordin (1960) was in the low range (43.4 ± 10%; range 24.9 - 73.7%; n=61).

Although the evaluation of the two signs most frequently encountered (ie ground glass appearance of the skull and spongiosis of the compacta of the phalanges) depends heavily on subjective criteria and requires good roentgenological technique, they are apparently a very sensitive index of bone disease and tend to reflect adequately its progression in repeated examinations. Both signs seem to deserve more attention.

**BONE HISTOLOGY**

Bone histology was evaluated quantitatively in iliac crest biopsy specimens. Undecalcified sections, stained after Masson-Goldner, were analysed by micromorphometry (Schenk and Merz, 1969). Details of the method are given elsewhere (Krempien & Ritz, 1971).

Bone volume (volumetric density) tended to be high (Table I) both in uraemic and in dialysed uraemic patients (Ireland et al, 1969). Thus there was no evidence of bone atrophy in dialysed patients (Kuhlencordt et al, 1971). This is the more remarkable, since bone mineral content of the calcaneus, measured by in vivo densitometry, was distinctly decreased.

The ratio of bone surface to bone volume, the specific surface, that reflects the complexity of the trabecular surface, was virtually unchanged.

The fraction of trabecular surface occupied by Howship lacunae was increased both in uraemic and in dialysed uraemic patients, but decreased with increasing length of dialysis (Table III). Although this finding might be
Table I. Micromorphometric measurements in dialysed uraemic patients (iliac crest biopsy)

<table>
<thead>
<tr>
<th></th>
<th>control (n=15)</th>
<th>uraemic (non-dialysed) (n=18)</th>
<th>uraemic (dialysed) (n=47)</th>
<th>duration of dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>3 m</td>
</tr>
<tr>
<td>Volumetric density (V_v)</td>
<td>24.5±7.62</td>
<td>31.2±9.5</td>
<td>30.8±10.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>32.9±9.6</td>
<td>35.0±12.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>29.4±4.7</td>
<td></td>
</tr>
<tr>
<td>Osteoid volume (V_o)</td>
<td>0.946±0.77</td>
<td>5.14±5.3</td>
<td>5.46±6.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.98±6.1</td>
<td>4.49±3.83</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4.95±4.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.48±2.96</td>
<td></td>
</tr>
<tr>
<td>Osteoid volume (Vob)</td>
<td>5.89±8.78</td>
<td>11.4±7.3</td>
<td>16.7±17.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>21.7±17.3</td>
<td>21.8±26.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14.4±3.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7.77±9.3</td>
<td></td>
</tr>
<tr>
<td>Osteoid surface (OS)</td>
<td>18.3±8.99</td>
<td>50.3±25.2</td>
<td>52.9±21.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>50.3±25.2</td>
<td>31.1±16.2</td>
<td></td>
</tr>
<tr>
<td>Active osteoid (OSa)</td>
<td>30.0±27.7</td>
<td>34.9±22.0</td>
<td>32.4±23.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active Howship lacunae</td>
<td>(HO)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.43±1.35</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Specific surface (S/V)</td>
<td>18.5±6.07</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mm/mm²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 fraction of bone volume (percent of total volume)
2 mean ± 2 standard deviations
3 fraction of total volume
4 fraction of bone volume
5 fraction of total trabecular surface
6 fraction of osteoid covered by osteoblasts
7 fraction of trabecular surface covered by active Howship lacunae
subject to the criticism that patients with hyperparathyroidism were eliminated from the group by parathyroidectomy, it shows at least that on an average fibroosteoclasia does not progress markedly under the conditions of haemodialysis used in our patients (dialysate [Ca$^{++}$] 2.4 mM - 3.6 mM). Probably progressive stimulation of the parathyroids is arrested (Johnson et al, 1969) when serum calcium levels are raised by haemodialysis (Cohen & Kaye, 1969).

Although active Howship lacunae apparently decreased during prolonged RDT, there was a significant fraction of dialysed patients who showed highly increased osteoclasia which tended even to increase at each observation; these patients presented clinically the syndrome of so called autonomous hyperparathyroidism.

The fraction of trabecular surface covered by unmineralised osteoid and the fraction of bone volume represented by osteoid were increased in uraemic and dialysed uraemic patients. Fractional osteoid volume (Vob) tended to decrease somewhat with increasing length of dialysis (Table III); this would indicate better mineralisation of osteoid in dialysed patients. There was no significant decrease of the fraction of trabecular surface covered by osteoid.

On the contrary there was a good correlation between total duration of known uraemia and fractional osteoid volume in non dialysed uraemic patients; patients with longer uraemia tended to have more osteoid.

It is interesting to note that active osteoid, ie the fraction of osteoid seams with active osteoblasts synthesizing bone matrix, was unchanged in uraemia. However, because osteoid surface increased in renal insufficiency the absolute amount of active osteoid increased likewise. The number of osteocytes per unit bone area was increased in undecalcified bone sections. Through microradiography increased diameters of osteocytic areas (periosteocytic demineralisation) were found. This finding presumably represents the morphological equivalent of periosteocytic osteolysis induced by PTH (Belánger et al, 1963).

**SERUM CHEMISTRY**

Serum chemistry (ie Ca, P, alkaline phosphatase) showed little correlation with bone histology and was not of predictive value in the individual patient.

**SERUM PARATHORMONE CONCENTRATIONS**

Serum PTH levels were markedly elevated in our patients (1268±736 pgEq bovine PTH/ml; normal < 400 pgEq/ml).

There was a marginal increase of specific surface with rising serum PTH levels (Table II), pointing to a higher complexity of trabecular surface. As expected there was also an increase in the surface fraction covered by Howship lacunae (Table III (3)). With rising PTH levels both osteoid volume
Table II. Relation between serum PTH levels and micromorphometric bone parameters in dialysed patients

<table>
<thead>
<tr>
<th>Serum PTH (pg Eq bovine PTH/ml)</th>
<th>400-800</th>
<th>800-2000</th>
<th>&gt; 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 12</td>
<td>4</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Volumetric density (V\textsubscript{v})</td>
<td>35.2±14.4</td>
<td>33.9±6.4</td>
<td>33.1±6.8</td>
</tr>
<tr>
<td>Specific surface (S/V)</td>
<td>17.7±5.97</td>
<td>18.1±4.78</td>
<td>19.6±9.49</td>
</tr>
<tr>
<td>Osteoid volume (V\textsubscript{o})</td>
<td>2.44±2.91</td>
<td>7.58±7.8</td>
<td>8.09±6.23</td>
</tr>
<tr>
<td>Osteoid surface (OS)</td>
<td>37.1±24.4</td>
<td>55.9±24.1</td>
<td>52.9±27.3</td>
</tr>
<tr>
<td>Active Howship lacunae (HO)</td>
<td>4.75±3.64</td>
<td>9.79±4.65</td>
<td>6.46±2.44</td>
</tr>
<tr>
<td>Osteocytic density \textsuperscript{1}</td>
<td>1.72±0.487</td>
<td>2.11±0.834</td>
<td>2.84±1.67</td>
</tr>
<tr>
<td>Osteocytic area \textsuperscript{2}</td>
<td>-</td>
<td>385±57.1</td>
<td>588±115</td>
</tr>
</tbody>
</table>

1 osteocytes / 20,000 \(\mu^2\)
2 \(\mu^2\) (a. b. \(\pi\))

Table III. Correlation Table

Relation between duration of dialysis (x = number of months) and
1. active Howship lacunae (y = % surface)
   \(y = 7.13 - 0, 162 (x - 16.7); p < 0.05\)
2. osteoid volume \(V\textsubscript{o}\) (y = % bone volume)
   \(y = 17.1 - 0.282 (x - 16.6); p < 0.10\)

Relation between serum PTH levels (x = pg Eq bovine PTH/ml) and
3. active Howship lacunae HO (y = % surface)
   \(y = 7.8 + 0, 000 656 (x - 1295)\)
4. osteoid volume \(V\textsubscript{o}\) (y = % bone volume)
   \(y = 15.9 + 0.00158 (x - 1377)\)
5. osteocytic density (y = osteocytes / 20,000 \(\mu^2\))
   \(y = 2.139 + 0, 000 389 (x - 1228); p < 0.05\)
6. osteocytic area (y = \(\mu^2\))
   \(y = 413 + 0, 102 (x - 1411); p < 0.05\)

(Table III (4)) and osteoid surface increased. This might signify either that higher PTH levels are required in severe osteomalacia to overcome resistance to the hypercalcaemic effect of PTH or that PTH leads to the appearance of severely demineralised areas staining as osteoid. Both the number of osteocytes per unit bone area (Table III (5)) and the average osteocyte area (Table III (6)) measured in microradiographic preparations increased with rising levels of serum PTH levels. Both parameters seem to be a good index of the PTH action on bone and should be evaluated routinely in bone histology of uraemic subjects.

The strikingly good correlation between serum PTH levels and various histological parameters in the spongiosa of uraemic bone would argue
against a significant degree of resistance to the fibroosteoclastic action of PTH on bone in uraemia.

ACKNOWLEDGMENTS

This study was supported by the Deutsche Forschungsgemeinschaft. We thank Drs Schäfer (Berlin), Malluche (Frankfurt), Vonend (Freiburg), Schütterle (Giessen), Henning (Göttingen), Bünzer (Hamburg), Traut (Hamburg), Mecke (Karlsruhe), Thönis (Kassel), Sieberth (Köln), Strauch (Mannheim), Lange (Marburg), Schulz (Nürnberg), Würz (Stuttgart), Bunde (Tübingen), Klötsch (Würzburg), von der Nahmer (Wuppertal) for cooperation and help.

REFERENCES

Ritz, E., Krempien, B., Kuhn, H. and Heuck, F. (1971a) Israel Journal of Medical Science, 7, 520
A Fournier (Paris): I would like to ask what dialysate calcium concentrations were used in the different centres?

Ritz: Calcium was 2.5 to 3.0 mEq/l in the centres studied.

Fournier: But was it the same in all the centres?

Ritz: No, it was not.

Fournier: I think it would have been useful to see if bone resorption would decrease greater in the centres with a higher dialysate calcium than in the centres with the lower dialysate calcium. At the Mayo Clinic we showed quite a marked difference between the two groups. We compared the evolution of bone resorption on two successive bone biopsies; in a group of patients dialysed against rather a low dialysate calcium (less than 5.7 mg/100 ml) with a group dialysed against a higher calcium (6.0 mg/100 ml). Five out of six patients in the low calcium group showed an increase in bone resorption while the sixth showed no significant change. In contrast, all the patients in the high calcium group showed a decrease in bone resorption. I think it is important to take the dialysate calcium concentration into account.

Ritz: I quite agree with your comments and am well aware of your studies. This was the interpretation I had given to the fact that osteoclastic resorption seems to decrease with increasing length of dialysis. It is extremely difficult in retrospect to do these correlations because both calcium concentrations vary at varying times. This should be done in prospective studies, and we are actually performing such a study.

Fournier: In the paper you wrote with O’Riordan in the Quarterly Journal of Medicine, you showed data which did not support the idea that hyperparathyroidism was a cause of bone disease. Are your recent data rather inconsistent with these former ideas?

Ritz: In the paper with O’Riordan, a group with clinical bone disease was compared with a group without clinical bone disease and there was no difference in serum parathyroid hormone levels. I think that bone histology is a much more sensitive index than clinical bone disease, and that the label of clinical bone disease does not reflect accurately the action of serum parathyroid hormone on bone unless you have gross osteitis fibrosa.
W WALDHAUSEL (Vienna): I am impressed by your ability to measure parathyroid hormone (PTH). We have had severe problems in measuring PTH in patients with parathyroid adenoma, and have to massage the parathyroid glands to get high values in the draining blood. What were your PTH levels in the patients who had had parathyroidectomies? Did you get zero values?

RITZ: They were below 20. The upper normal range is 400.

P REINSCHKE (Berlin, DDR): In our unit, among 15 patients undergoing regular dialysis treatment for more than two years we have seen only one case with severe vascular and soft tissue calcification. This was a 39 year old man, with chronic renal failure caused by glomerulonephritis. He had severe hyperparathyroidism before starting dialysis treatment in March 1969, and although serum levels of phosphorus and calcium became normal at 3.4 mg/100 ml and 10.2 mg/100 ml respectively during treatment with aluminium hydroxide, his serum alkaline phosphatase level stayed increased at more than 100 i.u. It seems to us remarkable that the most prominent manifestations of periarticular calcium deposition occurred in the right hand, distal to the Cimino fistula. Perhaps in certain cases local circulatory disturbances may precipitate the occurrence of calcium deposits.