Quantitative Bone Histology in Acute Renal Failure

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Osteodystrophy in chronic renal failure is well known. Radiological signs have been found before haemodialysis; metastatic calcification and clinical symptoms of bone disease are familiar in chronically haemodialysed patients. Histological examination of bone disease have shown progressive demineralisation, osteomalacia and signs of hyperparathyroidism. The aetiology of bone disease is a combination of hyperphosphataemia, a decrease of ionized calcium, negative calcium balance, functional vitamin D deficiency with disappearance of 1-25 Dihydrocholecalciferol, and elevated plasma parathormone, probably partially inactivated because of persistant hypocalcaemia. The study of each of these factors is difficult in chronic renal failure.

Acute renal failure (ARF) where the onset of renal failure is well known, supplies a pathological model which allows the study of different successive stages of renal osteodystrophy.

Table I. Clinical data in ten patients with acute renal failure (ARF). IVC = intravascular coagulation

<table>
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<tr>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Anuria days</th>
<th>Haemodialysis</th>
<th>Clinical aetiology</th>
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<td>M</td>
<td>15</td>
<td>8</td>
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<tr>
<td>BS</td>
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<td>F</td>
<td>0</td>
<td>4</td>
<td>IVC post abortum</td>
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<tr>
<td>KY</td>
<td>42</td>
<td>F</td>
<td>0</td>
<td>5</td>
<td>intoxication: biliary obstruction</td>
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<tr>
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<td>55</td>
<td>F</td>
<td>12</td>
<td>peritoneal D</td>
<td>glomerulo N</td>
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<tr>
<td>GO</td>
<td>41</td>
<td>F</td>
<td>12</td>
<td>peritoneal D</td>
<td>septicaemia</td>
</tr>
<tr>
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<td>42</td>
<td>F</td>
<td>0</td>
<td>8</td>
<td>shock</td>
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<tr>
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<td>22</td>
<td>F</td>
<td>5</td>
<td>chronic</td>
<td>cortical necrosis</td>
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</table>

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METHODS

(a) Ten patients with acute renal failure have been studied. Clinical data are reported in Table I. Nine patients are still alive.
(b) Bone biopsies were obtained by transfixing the iliac bone using Bordier's trocar. The trephine provided a cylindrical sample limited in height by the internal and external cortices which protect the integrity of the spongy bone. Two bone cylinders removed at the same time during the biopsy procedure

Figure 1. Evolution and chronology of histological and biological data in one case
were either decalcified or treated without decalcification. The first was cut in 32 serial sections; 5 microns thick, the second in 8 serial sections of 8 microns. Thirty-four biopsies were obtained thus from ten patients.

Different parameters were studied: the absolute bone volume of spongy iliac bone or 'bone mass', the relative osteoid volume of iliac cancellous bone, the trabecular osteoclastic resorption surface, and the size of peristeocytic lacunae. In six cases, the calcification rate was measured after tetracycline labelling.

(c) The first biopsy was obtained 5 to 12 days after the onset of renal failure, then repeated every week until the recovery of renal function (creatinine clearance above 30ml/min). The day of the biopsy total calcium (direct complexometry, mean value 9.5.), ionized calcium (direct electometric technics by selective electrode, mean value 4mg/100ml or 53% total calcium) and alkaline phosphatase (King Armstrong modified method, mean value <13 μ) were measured (Figure 1).

RESULTS
(a) Evolution of biological parameters appears in Figure 2. During the first week, total calcium decreased to 7.5, the ionized calcium to 2.1 and the phosphorus increased to 7.6mg/100ml. These values return to normal after recovery of renal function.

(b) Quantitative morphological data of bone histology: There is a significant hyperosteoclasia; a resorption surface of 6.8%±3.1 is formed in the biopsy showing the maximum variations compared with 3.2%±0.9 in the controls (p<0.001) and 9.1%±5 in primary hyperparathyroidism (Figure 3).

The size of periosteocyte lacunae is increased since the mean lacunar cross sectional area can be contained in a 56.4±8.8 square micron

Figure 2. Evolution of biological data in ten cases of ARF. iv = initial value, mv = maximal variation, tv = value at the end of the disease
Figure 3. Trabecular osteoclastic resorption surfaces. 62 normal values, 10 acute renal failure, 40 primary hyperparathyroidism

Figure 4. Size of the periosteocytic lacunae. 94 normal values, 10 acute renal failure, 41 primary hyperparathyroidism
Figure 5. Relative osteoid volume and osteoid area in seven patients with acute renal failure. In two cases symptoms of osteomalacia are found.

Figure 6. Calcification rate in cortical and spongy bone in 6 patients with ARF. In one case a decrease of accretion is shown at the fourth week.
rectangle whereas this parameter is 50.6 ± 2 in the controls and 65.5 ± 8.5 in pHPT (Figure 4). Thus in nine cases out of ten, there are significant increase of the osteoclastic resorption surfaces, and of the size of periosteocytic lacunae.

The relative osteoid volume was evaluated in 22 biopsies from 8 patients. Comparison with the average does not show a significant difference because the osteoid volume is 1.64% ± 1.22 in the controls compared with 1.24% in patients. It appears significantly increased in only two cases to 4.5 and 7.1%. However osteoid area measurements in 18 biopsies from eight patients are only increased in one case (Figure 5). The calcification rate, after repetitive tetracycline labelling, was measured in 8 biopsies from 6 cases, and found normal in 7 cases, at 1.25 ± 0.7 micron per day. It was decreased in a late biopsy taken during prolonged anuria (Figure 6).

DISCUSSION

Uraemic osteodystrophy remains one of the major problems of chronic renal failure. At the onset of haemodialysis the bone manifestations are a decrease of bone mass, a progressive fibrosis filling numerous Howship lacunae, a dramatic osteomalacia with an increase of the osteoid volume, of the osteoid area, and of the thickness of the osteoid borders.

Sequential bone biopsies in acute renal failure are able to show the first symptoms of renal osteodystrophy. There is an early hyperparathyroidism. Osteoclastic resorption surfaces increase during the first week, then decrease after the 20th day and return to normal.

It remains at high values in only one case of cortical necrosis with definitive anuria. A similar evolution of the size of periosteocytic lacunae is found. It is elevated in the first and second biopsies, then returns to normal; it remains elevated in the case of definitive anuria, (Figure 7).

There is no sign of osteomalacia until the 20th or 25th day. However, in three cases of prolonged anuria in the fourth week there is an increase of osteoid volume, of osteoid area and thickness, and, in one case, a significant decrease of calcification rate (Figure 8).

The onset of renal osteodystrophy observed in ARF is thus characterised by signs of hyperparathyroidism ten to twenty days before osteomalacia. Parathormone increases quickly and early whereas the functional disease of vitamin D deficiency appears later.

SUMMARY

Ten patients suffering from acute renal insufficiency of miscellaneous aetiology were observed and their bone disease studied by sequential bone biopsies every week, until the recovery of kidney function.
Figure 7. Evolution of bony symptoms of hyperparathyroidism. The trabecular osteoclastic resorption surfaces and the size of the periosteocytic lacunae increase, then return to normal values with the recovery of renal function except in one case of cortical necrosis.

Figure 8. Absence of osteomalacia at the onset of ARF. Increase of osteoid volume after the fourth week in three cases.
An early increase of the osteoclastic resorption surface to 6.8% ± 3.1 (normal value 3.2 ± 0.9) and of the size of periosteocytic lacunae to 56.4 ± 88 (normal value 50.6 ± 2) was found.

These values were highest during the first ten days and decreased to normal when renal function returned to normal.

Osteomalacia appeared only when anuria was prolonged beyond the third or the fourth week, with an increase of the osteoid volume and area, and a decrease of the calcification rate after tetracycline labelling.

REFERENCES

Bordier, P., Matrajt, H., Miravet, L. and Hioco, D. (1964) Pathologie et Biologie, 12, 23

OPEN DISCUSSION

E RITZ (Heidelberg): You mentioned in your presentation that the surface fraction covered by osteoid would be an indication of the presence of osteomalacia. I should like to challenge that statement. If you increase the growth rate of osteoid seam, you are bound to see more osteoid even if there is no delay of mineralisation rate. Even in primary hyperparathyroidism without any change in the mineralisation rate, you do see more osteoid.

You can measure the rate of mineralisation in cortical bone, as the geometry of bone relative to the plane of section is constant. However, in spongy bone, the plane of section changes relative to the trabeculae. We do not have the necessary geometry to calculate the rate of mineralisation because one lacks the constancy of the third dimension. Would you care to comment on this?

ZECH: The histological examples that I have quoted are examples of chronic renal failure not acute renal failure. There is no osteomalacia in acute renal failure. The mineralisation rate was only measured in cortical bone.