OSTEOMALACIA IN CHRONIC RENAL
FAILURE BEFORE DIALYSIS*

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Summary

Bone biopsies taken from 327 patients before the start of dialysis have been
correlated with clinical and biochemical findings to test various theories about
the aetiology of osteomalacia. Two groups of patients, 100 with osteomalacia
and 100 with pure osteitis fibrosa, have been compared in detail. Osteomalacia
is associated with chronic pyelonephritis or obstruction as primary renal disease,
and with acidosis, hypocalcaemia and normophosphataemia (as opposed to
hyperphosphataemia). We have found no association between osteomalacia and
known duration or severity of uraemia and in a small series of observations we
have not confirmed previous reports of a close association between osteomalacia
and depressed plasma 25(OH) cholecalciferol values.

Introduction

The cause of osteomalacia in chronic renal failure (CRF) before dialysis is
uncertain. Well recognised causes like florid vitamin D deficiency, hypophos-
phataemia and anticonvulsant therapy account for only a small proportion.
Previous authors have suggested that predisposing factors may include:

1. Primary renal diseases that affect the medulla or/and cause acidosis out of
   proportion to loss of glomerular filtration rate [1–3].

2. Slowly progressive renal disease causing prolonged mild uraemia [4].

3. Subclinical vitamin D deficiency, revealed only by a low, or low normal,
   serum 25(OH)D₃ value [5–7].

4. Relative phosphate deficiency without hypophosphataemia [8].

To test these and other hypotheses, we have reviewed our bone biopsies,
taken from patients approaching the need for dialysis and transplantation over
the last 15 years.

* Presented by Dr N Muirhead on behalf of Dr F Mora Palma
**Materials and methods**

Between January 1967 and April 1982, 327 bone biopsies were taken from patients in CRF who had not undergone any form of dialysis. They were obtained by the transiliac technique and sectioned and stained as previously described [9, 10]. Since only a few patients had been labelled with tetracycline, osteomalacia was diagnosed on the basis of: (a) increased proportion of bone area and surface occupied by uncalcified osteoid, combined with a reduction in the active ossification front, stained with toluidine blue; (b) an increase in the number of uncalcified osteoid lamellae beyond the normal [1—4].

By these criteria, 112 biopsies showed osteomalacia which was always combined with osteitis fibrosa (OM/OF), 175 showed osteitis fibrosa only (OF) and 40 showed neither lesion (nil). These whole groups were compared in terms of primary renal diagnosis. Two comparison groups of 100 were then selected from the OM/OF and OF groups, to provide sufficient patients with each of the major

<table>
<thead>
<tr>
<th>TABLE I. Acidosis</th>
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<tbody>
<tr>
<td>Bicarbonate (mmol/L)</td>
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<tr>
<td>Severe acidosis (&lt; 16)</td>
</tr>
<tr>
<td>Moderate acidosis (16—20)</td>
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<td>Mild acidosis (&gt; 20)</td>
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<tr>
<th>TABLE II. Hypocalcaemia</th>
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<tr>
<td>Total serum calcium (mmol/L)</td>
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<tr>
<td>Severe hypocalcaemia (&lt; 2.00)</td>
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<tr>
<td>Mild hypocalcaemia (2.00—2.21)</td>
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<tr>
<td>Normocalcaemia (&gt; 2.22)</td>
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| Ionised calcium (mmol/L) | OM/OF number | % | OF number | % | 2 p |
| Severe hypocalcaemia (< 1.00) | 21 | 58 | 12 | 22 | < 0.001 |
| Mild hypocalcaemia (1.00—1.15) | 9 | 25 | 21 | 39 | NS |
| Normocalcaemia (> 1.16) | 6 | 17 | 21 | 39 | < 0.025 |

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diagnoses to allow comparison of other characteristics, diagnosis by diagnosis. The 100 OF patients were selected also on the basis of adequate documentation and as far as possible similar era of biopsy. The last objective was only partially achieved; 18 per cent of the OM/OF group but only eight per cent of the OF group were biopsied between 1967 and 1971, when the procedure was used largely for the investigation of symptomatic bone disease. These 'matched' groups of 100 were compared in terms of clinical and biochemical characteristics (Tables I and II). Biochemical data represent the average results obtained when attending the pre-dialysis clinic before biopsy; the mean (± SD) observation periods were 4.1 ± 1.9 months for the OM/OF group and 4.3 ± 1.8 months for the OF group. The two groups were also comparable in age: mean (range) being 43.8 (4–78) years in the OM/OF group and 41.6 (4–67) years in the OF group, sex ratio, and known duration of uraemia before biopsy: mean ± SD 68.8 ± 41.9 months for OM/OF and 63.5 ± 45.7 for OF.

Results

Primary diagnosis

The primary renal diagnoses in the whole 327 patients are listed in Table III. The diagnosis of chronic pyelonephritis was based on radiology or histology of whole kidneys in 54/58 cases and that of glomerulonephritis was confirmed by histology in 68/82. Clinical diagnoses were only accepted when very well supported by

<table>
<thead>
<tr>
<th>Primary renal disease</th>
<th>OF/OM</th>
<th>2 p</th>
<th>OF</th>
<th>2 p</th>
<th>nil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>112</td>
<td></td>
<td>175</td>
<td></td>
<td>40</td>
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<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>8.0</td>
<td>&lt; 0.001</td>
<td>30.3</td>
<td>&lt; 0.05</td>
<td>50.0</td>
</tr>
<tr>
<td>Chronic pyelonephritis</td>
<td>26.8</td>
<td>&lt; 0.2</td>
<td>14.8</td>
<td>&lt; 0.05</td>
<td>5.0</td>
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<tr>
<td>Polycystic disease</td>
<td>16.1</td>
<td>NS</td>
<td>12.6</td>
<td>NS</td>
<td>10.0</td>
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<tr>
<td>Obstructive uropathy</td>
<td>16.1</td>
<td>&lt; 0.05</td>
<td>7.4</td>
<td>NS</td>
<td>5.0</td>
</tr>
<tr>
<td>Renal vascular disease*</td>
<td>0.0</td>
<td>&lt; 0.001</td>
<td>8.0</td>
<td>NS</td>
<td>10.0</td>
</tr>
<tr>
<td>Analgesic nephropathy</td>
<td>5.3</td>
<td>NS</td>
<td>2.8</td>
<td>NS</td>
<td>2.5</td>
</tr>
<tr>
<td>Miscellaneous†</td>
<td>7.1</td>
<td>NS</td>
<td>8.0</td>
<td>NS</td>
<td>15.0</td>
</tr>
<tr>
<td>Uncertain</td>
<td>20.5</td>
<td>NS</td>
<td>16.0</td>
<td>&lt; 0.02</td>
<td>5.0</td>
</tr>
</tbody>
</table>

* Includes primary hypertension
† Includes diabetic nephropathy, systemic lupus, polyarteritis, gout, tuberculosis, amyloidosis, oxalosis, Fabry's disease, interstitial nephritis; no individual diagnosis significantly more numerous in any one subgroup
data so the ‘Cause Uncertain’ category was larger than in the EDTA registry.

Chronic pyelonephritis and obstructive nephropathy were significantly over-represented in the OM/OF group while glomerulonephritis and renal vascular disease (including primary hypertension) were highly significantly over-represented in the OF group.

**Acidosis**

The severity of acidosis was assessed in the two matched groups of 100 patients with OM/OF and OF, by plasma bicarbonate. Severe acidosis was defined in advance as $< 16$ mmol/L, moderate acidosis as $16 - 20$ mmol/L and mild acidosis as $> 20$ mmol/L. The results are shown in Table I. Severe acidosis was very significantly associated with OM/OF and mild acidosis with OF. The effect of acidosis was also assessed for each of the major primary renal diseases. Plasma bicarbonate was significantly lower in those with OM/OF than in those with OF whether the primary diagnosis was obstructive uropathy ($14.8$ versus $18.4$ mmol/L, $2p < 0.05$) or chronic pyelonephritis ($14.7$ versus $17.9$ mmol/L, $2p < 0.05$) and the difference approached significance when the diagnosis was glomerulonephritis ($15.1$ versus $17.7$ mmol/L, $p < 0.05$) or polycystic kidneys ($14.5$ versus $16.7$ mmol/L, $p < 0.05$). (It is a moot point whether $2p$ or $p$ is the correct figure to quote in this study which was in part aimed to test an existing hypothesis that acidosis was associated with osteomalacia.)

**Hypocalcaemia**

Hypocalcaemia was defined in advance as severe if serum total calcium was $< 2.0$ mmol/L or serum ionised calcium was $< 1.0$ mmol/L, and mild if serum total calcium was $2.00 - 2.21$ mmol/L or serum ionised calcium was $1.00 - 1.15$ mmol/L. The results for the matched groups of 100 are shown in Table II. There were strong associations between severe hypocalcaemia and OM/OF and between normocalcaemia and OF. These associations were stronger for total than for ionised serum calcium because of the larger number of observations; serum ionised calcium measurement was introduced about half-way through the survey period.

The influence of hypocalcaemia was also examined for each of the major primary renal diagnoses. Total serum calcium was significantly lower in the OM/OF group in chronic pyelonephritis ($1.85$ versus $2.24$ mmol/L, $2p < 0.001$), obstruction ($1.89$ versus $2.23$ mmol/L, $2p < 0.01$), polycystic disease ($1.77$ versus $2.11$ mmol/L, $2p < 0.005$) and glomerulonephritis ($1.87$ versus $2.10$ mmol/L, $2p < 0.05$). Serum ionised calcium was also lower in the OM/OF group throughout but the difference was only significant for polycystic disease, again reflecting smaller numbers of observations.

**Phosphataemia**

Plasma phosphate was divided in advance into normal ($0.80 - 1.40$ mmol/L), mildly raised ($1.41 - 1.99$ mmol/L) and severely raised ($2.00$ mmol/L and above);
no patient had hypophosphataemia. Normophosphataemia was associated with OM/OF (29% versus 8% in OF, 2p < 0.001) and severe hyperphosphataemia with OF (54% versus 32% in OM/OF, 2p < 0.005). The effect of plasma phosphate was also assessed for each major primary renal disease. Plasma phosphate was lower in the OM/OF group in each of the four main diagnoses but the difference was significant only for chronic pyelonephritis (1.67 versus 2.13mmol/L, 2p < 0.02).

Severity and duration of uraemia

The OM/OF and OF groups did not differ significantly in known duration of uraemia, either in toto or in any of the four major diagnostic subgroups. Mean plasma creatinine followed no consistent pattern; it was significantly higher in the OF group in obstruction and polycystic disease but the difference was not significant for chronic pyelonephritis and the pattern was reversed in glomerulonephritis.

25(OH) cholecalciferol

A competitive protein-binding assay for 25(OH) cholecalciferol has been available in Newcastle intermittently over the latter half of the period covered by this survey [11]. Measurements are therefore available from only a minority of the patients in the two comparison groups. They are displayed in Figure 1. The mean concentration is a little lower in those with OM/OF but there is wide overlap and the difference does not approach significance at the five per cent level.

![Graph showing serum 25OHD3 levels](image-url)

**Figure 1**
Discussion

Our study has confirmed several previous suggestions: OM is associated with primary renal diseases that affect the medulla, with acidosis, hypocalcaemia and normophosphataemia (as opposed to hyperphosphataemia). Our patients are selected since most of them were biopsied from the pre-dialysis clinic and those with the most fulminating disease bypass that clinic. With this proviso, we can find no association between severity or known duration of uremia and the presence of OM. Nor can we demonstrate from our limited material any association between the presence of OM and depressed plasma 25(OH) cholecalciferol values. It is therefore unlikely that the association of OM with medullary disease is merely a reflection of the slower course of renal failure in these diseases, than in glomerulonephritis. It is possible that it reflects impaired 1,25(OH)2 cholecalciferol production in these diseases and we are now investigating that possibility.

However, our observations that OM is strongly associated with severe hypocalcaemia and acidosis and has an association with relatively low plasma phosphate levels suggest that physicochemical factors affecting calcification may be all-important. The association of OM with medullary disease may largely reflect their tendency to cause acidosis and hypocalcaemia out of proportion to depression of glomerular filtration rate, which is borne out in our data. This may also explain why OM is a diminishing disease in Newcastle. The proportion of bone biopsies which showed OM was 1967–71, 70 per cent; 1972–1976, 29 per cent; 1977–1982, 33 per cent. This is partly, we suspect, because bone biopsy was performed predominantly for florid bone disease in the first period and OM is more likely to cause symptoms than OF. However, the continuing decline in the prevalence of OM may well reflect our increasing effort to correct acidosis and hypocalcaemia at the pre-dialysis clinic.

Acknowledgments

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References

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Open Discussion

OHNO (Japan) I would like to ask you about the concentration of PTH and 1,25(OH)D₃.

MUIRHEAD Unfortunately we have not had the opportunity of measuring plasma 1,25(OH)D₃ in these patients but we have embarked on a study in which we are measuring 1,25(OH)D₃ concentrations in pre-dialysis patients since it is obviously of some importance. There was no significant difference in parathyroid hormone concentrations between the two groups.

ROTTEMBOURG (Paris) How many of your patients with normal plasma phosphate or high plasma phosphate were consuming aluminium gel for phosphate binding because these can interfere with osteomalacia even prior to dialysis therapy.

MUIRHEAD Three per cent of those with osteomalacia and 20 per cent of those with osteitis fibrosa were taking aluminium hydroxide gel.

FOURNIER (Amiens) I would like to know what was the usual prophylactic treatment of your patients with chronic renal failure concerning calcium carbonate supplements and vitamin D supplements?

MUIRHEAD During this study calcium carbonate was used routinely but the patients were not receiving vitamin D supplements.