OSTEOMALACIA IN ELDERLY PATIENTS WITH FRACTURE OF THE FEMORAL NECK
A Clinico-pathological Study

D. H. R. JENKINS, J. G. ROBERTS, D. WEBSTER and E. O. WILLIAMS, CARDIFF, WALES

From the Departments of Orthopaedics and Pathology, University Hospital of Wales, Cardiff

The clinical and radiological features of established osteomalacia are well recognised. Chalmers (1970) drew attention to the frequency of subtrochanteric fractures of the femoral neck among those with osteomalacia, and Gallagher, Aaron, Nicholson, Longton and Nordin (1972) suggested that osteomalacia was seen more frequently in association with subtrochanteric fractures than with fractures through the neck.

The concept of subclinical osteomalacia predisposing to fracture in the region of the femoral neck has not been fully explored.

Low serum values of calcium and phosphate and high levels of alkaline phosphatase, together with a low calcium-phosphate product are the accepted, simply determined, biochemical features of the disease (Exton-Smith, Hodkinson and Stanton 1966). An increase in osteoid revealed by bone biopsy has been regarded as an essential feature in the diagnosis since its description by Pommer in 1885. Raina (1972) showed that the osteoid normally covered the entire bone surface except in areas of resorption and noted that the thickness of the osteoid layer varied at different sites in the same animal. Thus an increase in the volume of osteoid is likely to be a more reliable criterion of osteomalacia than an apparent increase in the area of surface covered by osteoid.

Apart from histological methods, there is no single test from which a diagnosis can be made. In order to establish an index of suspicion we have examined the incidence of biochemically defined osteomalacia and have compared this where possible with quantitative histology in an elderly population with fracture of the neck of the femur.

METHOD

Seventy-four patients over the age of seventy with fracture of the femoral neck admitted to the Cardiff Royal Infirmary were examined for evidence of osteomalacia. There were fifty-eight women and sixteen men in the two fracture groups of forty subcapital fractures (thirty-four in women and six in men) and thirty-four fractures in the region of the intertrochanteric line (twenty-four in women and ten in men). Blood samples were taken from the cubital vein without the use of a tourniquet, with the patient fasting, on the morning after admission. Serum calcium, inorganic phosphate, proteins and alkaline phosphatase were estimated. Treatment in all cases was by one of the established methods of operation. At operation bone samples were taken. In the initial fifteen cases in which internal fixation was used, the femoral cortical bone chips, removed in order to facilitate entry of the fixing device, were saved and preserved in buffered formalin. When the head was removed this was similarly preserved.

Iliac crest biopsies were carried out on fifty-nine patients without increasing the size of the primary incision. It was a simple matter to insinuate an 8-millimetre trephine with introducer through the muscle bulk overlying the lateral border of the ilium until the trephine could be felt subcutaneously. Full thickness biopsies were taken. Total ionised serum calcium was estimated by the use of the normogram of McLean and Hastings (1935) which relies on the binding ability of albumin for calcium.

Bone samples were sectioned and stained by von Kossa's technique. The measurement of osteoid volume made was based on the assessment of the percentage area of osteoid in at least ten fields in trabecular bone. The method used was the Image Analyser Television Scan...
Technique (Pearse 1972, Williams 1972). The degree of resorption was estimated by eye and represented as none, trace, +, ++ and +++.

Range of accepted normal values—The following values were taken as the normal range. Serum calcium: 91–107 milligrams/100 millilitres. Serum phosphate: 2.6–4.5 milligrams/

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<tr>
<th>TABLE I</th>
<th>Serum Biochemistry (Seventy-four patients)</th>
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<tbody>
<tr>
<td>Ca &lt; 9.0 mg/100 ml</td>
<td>PO₄ &lt; 2.6 mg/100 ml</td>
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<tr>
<td>Number of cases</td>
<td>35</td>
</tr>
<tr>
<td>Percentage</td>
<td>54</td>
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<tr>
<th>TABLE II</th>
<th>Total Number of Serum Biochemical Values Outside the Normal Ranges Indicated in Table I</th>
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<tbody>
<tr>
<td>Abnormals</td>
<td>0</td>
</tr>
<tr>
<td>Number of cases</td>
<td>20</td>
</tr>
<tr>
<td>Percentage</td>
<td>27</td>
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<tr>
<th>TABLE III</th>
<th>Mean Serum Biochemical Values Related to Fracture Groups</th>
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<tbody>
<tr>
<td>Ca²⁺</td>
<td>PO₄⁻⁻</td>
</tr>
<tr>
<td>Subcapital fracture</td>
<td>9.06</td>
</tr>
<tr>
<td>Trochanteric fracture</td>
<td>8.90</td>
</tr>
<tr>
<td>t</td>
<td>.94 insig.</td>
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<tr>
<th>TABLE IV</th>
<th>Resorption Estimates Related to Fracture Groups (Forty-four histological samples examined)</th>
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</thead>
<tbody>
<tr>
<td>Degree of resorption</td>
<td>Trace</td>
</tr>
<tr>
<td>Subcapital fracture</td>
<td>3</td>
</tr>
<tr>
<td>Trochanteric fracture</td>
<td>4</td>
</tr>
</tbody>
</table>

100 millilitres (Smith, Davis and Fourman 1960). Alkaline phosphatase—levels not in excess of 40 I.U. were regarded as normal (Babson, Greeley, Coleman and Phillips 1966). Calcium—phosphate product: it is suggested that a calcium-phosphate product of less than 27 is a valuable index of osteomalacia (Salvesen and Bøe 1953, Chalmers 1968). This was therefore recorded.

Histological assessment: Tha Aung (1970) established a range of normal osteoid values in iliac crest trabecular bone. In his groups of men and women over the age of fifty the mean volume of osteoid expressed as a percentage of the total volume is 0.15 per cent. The range of normal is taken as 0.15 per cent ±2 standard deviations which equals 0.15 per cent ±0.32 and thus the upper limit of normal is 0.47 per cent. We have taken 0.5 per cent as the upper limit of normal on the assumption that this gives a generous margin for instrument error.
Iliac crest trabecular bone showing osteoid (grey areas) in a frankly osteomalacic patient. (× 50.)

Resorption was assessed on an admittedly crude basis but in view of the comments of Raina (1972) it was thought worth while including.

RESULTS

There was no morbidity associated with venepuncture, nor were there any complications after biopsy. Iliac crest biopsies caused no discomfort to the patients, and use of the technique described avoided an extra incision. There was one death after operation. Examination of the initial fifteen femoral bone samples showed that the chips were totally unsuitable for quantitation because of the nature of the cortical bone and the small quantity of adjacent trabecular bone in the samples. Iliac crest biopsies were suitable for quantitation.

Biochemistry—There was a high incidence of abnormal findings (Table I). Thirty-five per cent had three or four abnormalities and 57 per cent had two or more (Table II). There was no significant difference in any group of biochemical values when the two fracture groups were compared (Student’s t-test) (Table III).

There was, as expected, a high degree of correlation between low total serum calcium levels and ionised calcium levels. Of the thirty-six (56 per cent) total calcium values less than 9 milligrams/100 millilitres there were thirty-five (54 per cent) ionised calcium values less than 5·9 milligrams/100 millilitres and only one in the normal range of 5·9–6·5 milligrams/100 millilitres. There were, however, a further two low ionised serum calcium values in the presence of normal total calcium levels.

Resorption—There was no significant difference between the degree of resorption for the two fracture series (Kolmogorov-Smirof test) (Table IV).

Osteoid volumes—Owing to the poor quality of the femoral bone specimens these were ignored. Of the remaining fifty-nine there were forty-five adequate biopsies of the iliac crest showing sufficient bone to assess osteoid volumes (Fig. 1). In five cases there were femoral head samples in addition to iliac crest biopsies and in every case there was a high degree of correlation.
of osteoid volumes between the head and crest. The forty-five iliac crest osteoid volumes,
expressed as a percentage of the total volume, are represented in Figure 2. The method
of expression relies on the theory of Delesse (1848) and enables an assessment of three-dimensional
findings to be made on a two-dimensional examination. One patient with subcapital and four
with trochanteric fractures were considered to have unequivocal histologically proven
osteomalacia (Fig. 2A). A second group of ten (Fig. 2B) had osteoid in excess of the upper limit
of normal and together these two groups comprise 30 per cent of the samples examined.
The third group of thirty (Fig. 2C) were within the normal range.

Comparison of biochemical and histological results—Nine of the fifteen patients with osteoid in
excess of the upper limit of normal (groups A and B) had three or more abnormal biochemical
results. Of the five considered to be grossly osteomalacic three had four abnormal findings.
Of the ten samples showing osteoid marginally in excess of normal (group B) three had less
than two abnormal values and five had three abnormal findings. However, in the biopsy-
proven non-osteomalacic group there were fourteen out of thirty with normal biochemistry
(one abnormality or none) and eight with three or more biochemical values outside the normal
range. Within the limits of the resorption estimation it is noteworthy that in the five with
the largest osteoid volumes resorption was recorded as \(++\) or \(++++\) and that in the thirty
with osteoid volumes within the normal range there were none with more than \(+\) recorded.

![Diagram](image)

**Fig. 2**
Iliac crest osteoid volumes (ordinate) expressed individually (abscissa) within
the two fracture groups. 0-5 per cent is regarded as the upper limit of normal
osteoid volume. Patients in group A are thought to be grossly osteomalacic;
those in group B to represent subclinical osteomalacia; and those in group C
to be within the normal range.

**DISCUSSION**

Our results suggest that a form of subclinical osteomalacia may be more common than
is normally supposed. Clearly the diagnosis rests on the acceptance of certain biochemical
and histological criteria in an established clinical situation.

Anderson, Campbell, Dunn and Runciman (1966) stated that simple biochemical tests
often gave equivocal results, and that of the three estimations we have undertaken, two might
be normal in the presence of osteomalacia. They made the important point that blood samples
must be taken from the fasting patient (as was done in our series).

Plasma calcium is in three forms—ionised, protein-bound and combined with citrate
and other organic acids. In normal plasma the ionised calcium is about 65 per cent of the total
and ranges from 5-9 to 6-5 milligrams/100 millilitres (Terepka, Toribara and Dewey 1958).
It is this fraction which is controlled by the parathyroid glands and is involved in all aspects
of calcium metabolism. Thus, in the pathological state, alterations in the plasma ionised calcium concentration are of major importance and variations in total calcium concentration will depend on the binding activity of the plasma albumin. The normogram of McLean and Hastings (1935), despite its recognised limitations, provides a value for the ionised calcium given values of total calcium and plasma proteins. In our groups, examination of the ionised calcium levels produced a greater number of abnormally low levels and emphasised the hypocalcaemic nature of our patients.

On the basis of the accepted simple biochemical criteria, our patients had a very high incidence of biochemically defined osteomalacia. Only 27 per cent could be considered entirely normal and 57 per cent had two or more abnormal findings. Certainly 35 per cent (with three or more abnormal values) had unequivocal "biochemical" osteomalacia and this figure is increased if the ionised calcium figures are also considered.

Chalmers (1970) drew attention to the frequency with which subtrochanteric fractures occurred in patients suffering from osteomalacia and confirmed his earlier comments about the occurrence of osteomalacia in elderly women (Chalmers, Conacher, Gardner and Scott 1967). Gallagher et al. (1972) also commented on the frequent occurrence of osteomalacia in association with fracture of the neck of the femur and they too suggested that it occurred more commonly in the intertrochanteric groups. Our findings confirm the impression of others that osteomalacia, diagnosed on simple biochemical tests, is in fact a common condition in the age group examined. Statistical analysis does not however reveal any difference between this occurrence in the two fracture groups.

A variety of methods have been applied to the measurement of osteoid and a variety of techniques have been advanced producing varying standards of normality (Chalmers, Barclay, Davison, MacLeod and Williams 1969). We have experienced difficulty in assessing osteoid in femoral bone and recommend that bone samples be removed from the iliac crest, while recognising that osteoid values in the facture site and biopsy site may not bear direct relationship to one another. Confusion is encouraged by the varying methods of expressing osteoid quantity. The amount of bone surface covered by osteoid in normal bone apparently varies (Kelly, Jowsey and Riggs 1965; Woods 1966; Raina 1972). Raina's (1972) comments suggest to us that what is abnormal is not so much the presence of osteoid, but its quantity. A method employing measurement of volume is therefore preferred and we have found this to be satisfactory.

How then can our results assist in the simpler diagnosis of this condition? Thirty per cent of the sample examined demonstrated histological osteomalacia (Fig. 2A and B) and 30 per cent had osteomalacia biochemically but there was little relationship between the two diagnostic methods. However, where there was no doubt about the histological diagnosis, findings gave added support. In the group exhibiting normal histology 55 per cent had two or more abnormal biochemical values suggesting that either the standard biochemical tests are of little value or that they indicate a subclinical form of the disease. The group showing marginal, although definitely abnormal, histology (Fig. 2B) may represent the next stage of subclinical progression towards the frank osteomalacic state demonstrated by our five patients with grossly abnormal osteoid values.

Can the routine tests be regarded as valuable in any way? Chalmers, Barclay, Davison, MacLeod and Williams (1969), using a different method and expression of quantity of osteoid, found that the calcium-phosphate product was low in 22 per cent of cases with osteoid values within the normal range and also low in 38 per cent of cases with osteoid values suggestive of osteomalacia. They found elevation of alkaline phosphatase to be of little value. Our results agree with Chalmers's recorded findings and emphasise the unreliability of isolated biochemical results. If anything, the biochemical findings were on the side of caution since only three of our biopsy-proven osteomalacic group had normal biochemistry and none of these was in the frankly osteomalacic subgroup.
The suggestion is therefore made that all patients with fracture of the neck of femur, irrespective of the type of fracture, should be screened on a biochemical basis initially. Where two or more abnormal values are found, biopsy of the iliac crest should be taken with a view to detecting subclinical osteomalacia.

SUMMARY
1. Seventy-four patients over the age of seventy with either subcapital or intertrochanteric fracture have been investigated for evidence of osteomalacia. To establish an index of suspicion the incidence of biochemically defined osteomalacia has been compared with quantitative histology in this group.
2. Whereas no significant difference in the incidence of the disease was noted in the comparison of subcapital with trochanteric fracture groups, there was a high incidence of osteomalacia overall. Furthermore, a subclinical form of the disease appears to exist.
3. The relevance of these observations is discussed with particular reference to the established diagnostic criteria of the condition.

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REFERENCES