Osteomalacia may be a contributory factor in some patients in the development of fractures of the femoral neck and complicate the subsequent management. The level of serum alkaline phosphatase is often valuable in the diagnosis of metabolic bone disease but rises after any uncomplicated fracture, and since such a rise may limit the diagnostic usefulness of this measurement in detecting osteomalacia its extent was assessed in 106 patients. In the majority serum levels were normal on admission, rising after seven to nine days to reach a maximum within a month after fracture. Elevated levels on admission were found in patients with osteomalacia, liver damage or where there had been a delay of several weeks between injury and admission. In a small number of patients normal levels on admission subsequently reached very high values, usually in association with comminution or instability of the fracture. Elevated levels persisted for six to twelve weeks after fracture, the major influence upon the level at this time being the maximum value achieved rather than the presence of osteomalacia. If patients are to be screened for osteomalacia, the alkaline phosphatase must be measured within the first week after a fracture to avoid the distorting influences of the fracture itself.

Several studies have drawn attention to the prevalence of osteomalacia in elderly patients with fractures of the femoral neck (Jenkins et al. 1973; O'Driscoll 1973; Aaron et al. 1974). This association is not only of pathogenic significance but has important therapeutic implications. For example, osteomalacic patients with bone pain and perhaps a myopathy are more difficult to mobilise, with all the disadvantages which this entails. Furthermore, prosthetic replacement or internal fixation may be more difficult in the poorly mineralised femur.

It is therefore important to identify such patients at an early stage after admission, so that treatment may be modified accordingly. Most studies have concentrated upon histological screening, but this is time-consuming and delays between diagnosis and beginning specific treatment are inevitable. A biochemical approach has obvious attractions because of its speed. Of the tests available, serum alkaline phosphatase activity has considerable potential because it is usually increased in osteomalacia (Fourman and Royer 1968). However, problems may arise because the level of alkaline phosphatase is also affected by the fracture itself. It is difficult to make allowance for this distorting effect because of the surprising lack of information on the magnitude and timing of this change after uncomplicated fractures.

It is the purpose of the present paper to describe these temporal changes after femoral fractures and to define some of the factors that may distort the normal pattern of response and thus impair its usefulness in the diagnosis of osteomalacia.

**Patients and Methods**

The study comprised 106 patients (twenty-four men and eighty-two women) over the age of fifty years admitted with femoral fractures in the five-month period from June 1976. It proved administratively impossible to study all patients, but no selection was made apart from excluding those with fractures through metastases and those younger patients admitted after road traffic accidents. The present sample

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represents 61 per cent of all femoral fractures in patients over the age of fifty admitted during this period.

Venous blood was taken for calcium, phosphate and alkaline phosphatase estimations as soon as possible after admission; further samples were taken on the third, fifth, ninth and fourteenth day, and then weekly until discharge. In seventy-four of the patients one of the early blood samples was taken fasting and corrected for serum albumin to a concentration of 46 grams per litre (Berry et al. 1973); the remaining samples were taken non-fasting.

Serum calcium was measured by atomic absorption spectrophotometry, phosphate by AutoAnalyzer, albumin by the bromocresol green method (Northam and Widdowson 1967) and serum alkaline phosphatase by the Hausamen technique (Hausamen et al. 1967).

Iliac crest biopsies were taken from a site three centimetres behind the anterior superior spine, using a Nicholson trephine. Sections were stained by the Goldner technique (Goldner 1937). A minimum of twenty-five fields on five sections were examined, using a twenty-five-point Zeiss integrating eyepiece at a magnification of \( \times 50 \). The osteoid area was expressed as a percentage of the total bone area, values above 5 per cent being considered to indicate osteomalacia (Szymendera, Heaney and Saville 1972).

RESULTS

Initial alkaline phosphatase. Serum alkaline phosphatase levels were available within three days of admission in 106 patients. Normal levels (6.5–27 King-Armstrong units or 46–190 international units per litre) were found in ninety-five patients, in fifty-eight of whom values were also available on each of the three subsequent occasions. Alkaline phosphatase activity remained substantially unchanged during the first week after a fracture, thereafter rising in the second and third weeks (Fig. 1).

Fifty-three patients with normal levels on admission survived or remained in hospital long enough for the alkaline phosphatase to reach a maximum. This was achieved within the first month in forty-five patients (Fig. 2), and was uninfluenced by age, sex or the level of alkaline phosphatase on admission.

Influence of fracture type and of treatment. Alkaline phosphatase activity in the ninety-five patients with normal values on admission was not affected by the type of fracture; levels of alkaline phosphatase tended to be lower in those with shaft fractures, but this difference was not statistically significant (Table I). The maximum value was not influenced either by the type of fracture or its subsequent treatment.

Table I. Influence of fracture type and of treatment

<table>
<thead>
<tr>
<th>Type of fracture</th>
<th>( n )</th>
<th>Initial* alkaline phosphatase</th>
<th>Maximum* alkaline phosphatase</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical</td>
<td>36</td>
<td>133.10±6.34</td>
<td>273.43±64.44</td>
<td>Prosthesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14</td>
<td>Fixation</td>
</tr>
<tr>
<td>Trochanteric</td>
<td>42</td>
<td>137.33±5.49</td>
<td>308.13±34.62</td>
<td>Nail-plate</td>
</tr>
<tr>
<td>Shaft</td>
<td>17</td>
<td>96.18±7.14</td>
<td>245.10±35.43</td>
<td>Traction</td>
</tr>
</tbody>
</table>

*Mean in iu/l±SE. (iu/7.1 = K-A units)

Although within the normal range on admission, alkaline phosphatase activity rose above 56 King-Armstrong units (400 international units) per litre in nine patients (Fig. 2). Further clinical details are given in Table II. The timing of the rise was no different from that seen in the majority of cases, but the one factor which seemed common to several patients in this group was comminution or poor alignment of the fracture. In several instances this was due to a delay between injury and admission, and in others severe osteoporosis led to difficulty in the insertion of a prosthesis. Age, sex, type of fracture and treatment did not seem important except in so far as they contributed to poor alignment or unstable fixation.

Unfortunately only three of these patients had biopsies taken and in the remainder osteomalacia cannot be definitely excluded. However, none had any biochemical evidence of osteomalacia in that admission levels of alkaline phosphatase, calcium and phosphate were all normal, and it seems unlikely that the high maximal values of alkaline phosphatase were a manifestation of metabolic bone disease.

Raised alkaline phosphatase on admission. Initial values above 27 King-Armstrong units (190 international units) per litre were found in eleven patients (Table III); several factors were implicated.

The patient in Case 10 was an alcoholic with supporting clinical and biochemical evidence of hepatic disease. A skeletal cause for the high alkaline phosphatase was excluded by a normal bone biopsy.

In each of Cases 11, 12 and 13 the injury causing the fracture had occurred one to three weeks before the patient's admission to hospital. It is likely that the rise in alkaline phosphatase was established by the time of
admission. Comparison with the mean values shown in Figure 1 suggested that the admission values were consistent with the age of the fractures. Iliac crest biopsy was normal in one of the patients; it was not performed in the remaining two.

The patient in Case 14 was admitted in severe congestive cardiac failure with hepatomegaly. Although bone biopsy was not performed the major component of the high alkaline phosphatase was almost certainly hepatic in origin.

In Cases 15 to 19 the patients had histologically proven osteomalacia (osteoid 20–70 per cent of total bone area), and all had had diets deficient in vitamin D. None had clinical or current biochemical evidence of hepatic disease, although one was an alcoholic.

The origin of the high alkaline phosphatase in the last patient (Case 20) was not found. None of the factors mentioned above appeared to be involved. No evidence of Paget’s disease was seen at the site of the fracture, but a radiological skeletal survey was not performed.

**Diagnostic significance of initial alkaline phosphatase.** Trephine biopsies of the iliac crest were available from forty-four patients, taken either at operation or as a

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**Table II. Patients with maximum alkaline phosphatase of more than 400 iu/l**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex and age</th>
<th>Fasting serum Ca (mmol/l)</th>
<th>Max. alk. phos. (iu/l)</th>
<th>Time of max. (weeks)</th>
<th>Bone biopsy</th>
<th>Fracture type</th>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F 83</td>
<td>1.40 1.08</td>
<td>525</td>
<td>2</td>
<td>—</td>
<td>Intertrochanteric</td>
<td>None</td>
<td>Operation refused. Poor alignment</td>
</tr>
<tr>
<td>2</td>
<td>F 88</td>
<td>2.45 1.11</td>
<td>550</td>
<td>2</td>
<td>—</td>
<td>Subcapital</td>
<td>Prosthesis</td>
<td>Satisfactory insertion and early mobilisation</td>
</tr>
<tr>
<td>3</td>
<td>F 73</td>
<td>2.35 1.14</td>
<td>420</td>
<td>3</td>
<td>—</td>
<td>Subtrochanteric</td>
<td>Traction</td>
<td>Severe osteoporosis</td>
</tr>
<tr>
<td>4</td>
<td>F 84</td>
<td>2.20 1.00</td>
<td>840</td>
<td>3</td>
<td>N</td>
<td>Intertrochanteric</td>
<td>Nail-plate</td>
<td>Good alignment. Comminuted fracture</td>
</tr>
<tr>
<td>5</td>
<td>F 87</td>
<td>2.34 0.84</td>
<td>440</td>
<td>3</td>
<td>N</td>
<td>Transcervical</td>
<td>Prosthesis</td>
<td>No obvious problems</td>
</tr>
<tr>
<td>6</td>
<td>F 76</td>
<td>2.39 0.85</td>
<td>1200</td>
<td>5</td>
<td>—</td>
<td>Subcapital</td>
<td>Nail-plate</td>
<td>Marked osteoporosis. Unstable fixation</td>
</tr>
<tr>
<td>7</td>
<td>F 81</td>
<td>2.23 0.90</td>
<td>484</td>
<td>4</td>
<td>N</td>
<td>Intertrochanteric</td>
<td>Nail-plate</td>
<td>Poor alignment of comminuted fracture</td>
</tr>
<tr>
<td>8</td>
<td>F 83</td>
<td>2.30 0.95</td>
<td>620</td>
<td>3</td>
<td>—</td>
<td>Subcapital</td>
<td>None</td>
<td>Normally chair bound. Poor alignment</td>
</tr>
<tr>
<td>9</td>
<td>F 87</td>
<td>2.25 1.10</td>
<td>446</td>
<td>2</td>
<td>—</td>
<td>Transcervical</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

*Non-fasting sample  
Bone biopsy: N = normal  
Conversions: Ca mmol/l x 4 = mg/100 ml  
P mmol/l x 3.1 = mg/100 ml  
Alk. phos. iu/l x 7.1 = K-A units

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**Table III. Patients with elevated alkaline phosphatase on admission**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex and age</th>
<th>Fracture</th>
<th>Initial alk. phos. (iu/l)</th>
<th>Bone biopsy</th>
<th>Other factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>M 52</td>
<td>Intertrochanteric</td>
<td>451</td>
<td>N</td>
<td>Alcoholic. Other liver function tests abnormal</td>
</tr>
<tr>
<td>11</td>
<td>F 79</td>
<td>Subcapital</td>
<td>295</td>
<td>N</td>
<td>Injury 10 days before first blood sample</td>
</tr>
<tr>
<td>12</td>
<td>F 82</td>
<td>Transcervical</td>
<td>465</td>
<td>—</td>
<td>Injury 3 weeks before admission</td>
</tr>
<tr>
<td>13</td>
<td>M 84</td>
<td>Subtrochanteric</td>
<td>279</td>
<td>—</td>
<td>Injury 2 weeks before admission</td>
</tr>
<tr>
<td>14</td>
<td>M 75</td>
<td>Transcervical</td>
<td>329</td>
<td>—</td>
<td>Gross congestive cardiac failure</td>
</tr>
<tr>
<td>15</td>
<td>F 92</td>
<td>Transcervical</td>
<td>248</td>
<td>OM</td>
<td>Dietary deficiency of vitamin D</td>
</tr>
<tr>
<td>16</td>
<td>F 79</td>
<td>Bilateral transverse</td>
<td>520</td>
<td>OM</td>
<td>Alcoholic. Dietary deficiency vitamin D</td>
</tr>
<tr>
<td>17</td>
<td>F 94</td>
<td>Intertrochanteric</td>
<td>411</td>
<td>OM</td>
<td>Dietary deficiency of vitamin D</td>
</tr>
<tr>
<td>18</td>
<td>F 80</td>
<td>Subcapital</td>
<td>227</td>
<td>OM</td>
<td>Dietary deficiency of vitamin D</td>
</tr>
<tr>
<td>19</td>
<td>F 78</td>
<td>Intertrochanteric</td>
<td>252</td>
<td>OM</td>
<td>Diet severely deficient in vitamin D</td>
</tr>
<tr>
<td>20</td>
<td>F 81</td>
<td>Intertrochanteric</td>
<td>630</td>
<td>N</td>
<td>No cause found</td>
</tr>
</tbody>
</table>

Normal alkaline phosphatase = 46–190 iu/l (6.5–27 K-A units)  
Bone biopsy: N = normal; OM = osteomalacia
ward procedure under local anaesthesia in those patients treated conservatively.

Osteomalacia was found in six patients, all but one of whom had elevated levels of alkaline phosphatase on admission (Fig. 3). Of those with histologically normal bone all but three also had normal levels of alkaline phosphatase. The factors believed to be implicated in the production of these abnormal values have already been discussed (Table III). The highest post-fracture value was of little diagnostic use because the level in the osteomalacic patients tended to remain relatively unchanged, while the rise occurring in normal patients resulted in a scatter of alkaline phosphatase levels which overlapped those found in osteomalacia (Fig. 3).

![Graph showing serum alkaline phosphatase levels](image1)

**Fig. 3** Alkaline phosphatase and bone histology (o) value at death or discharge.

**Fasting serum calcium and phosphate.** Fasting levels of serum calcium (corrected for albumin) and phosphate were available in seventy-four patients. Hypocalcaemia was found in five patients with initial alkaline phosphatases in the normal range (Fig. 4). The patient with the lowest value (7.8 milligrams per 100 millilitres; 1.95 millimoles per litre) had osteomalacia, but in only one of the remainder was a biopsy taken and this was histologically normal. Four of the six patients with osteomalacia were hypocalcaemic.

Fasting serum phosphate was low in all the patients with osteomalacia, but hypophosphataemia of comparable degree was found in about a quarter of those with normal biopsies.

**Decline in alkaline phosphatase.** Alkaline phosphatase levels were measured in forty-eight patients six to eight weeks after fracture. The majority were still raised, the most important factor determining the level being the prevailing maximum value (Fig. 5). Mildly elevated levels of alkaline phosphatase persisted in several patients when reviewed three months or more after fracture. Comparable figures were not available for those with osteomalacia because vitamin D therapy had been instituted once the diagnosis had been established.

![Graph showing relationship between fasting serum calcium and phosphate](image2)

**Fig. 4** Relationship between fasting serum calcium (●) and phosphate (○) and initial alkaline phosphatase.

![Graph showing relationship between maximum alkaline phosphatase and time after fracture](image3)

**Fig. 5** Relationship between maximum alkaline phosphatase and the value six to eight weeks after fracture.

**DISCUSSION**

Estimation of serum alkaline phosphatase appears to be a useful screening procedure for the detection of osteomalacia in the elderly patient presenting with a fracture of the femoral neck. The level of phosphatase activity remains unchanged in the first week after injury.
and appears unaffected by the type of fracture. Blood
taken on admission is likely therefore to have the same
diagnostic significance as it does in the uninjured patient
(Fourman and Royer 1968).

Not all patients with a raised level of alkaline
phosphatase have osteomalacia. Delay between injury
and admission is a most important factor resulting in a
high initial value. Since some of these elderly patients
are confused or overtly demented, and may normally be
relatively immobile, a femoral fracture may remain
unsuspected for days or weeks, during which time the
alkaline phosphatase level may become considerably
raised.

Another important factor is concurrent liver
disease or dysfunction due either to alcoholism or to
cardiac failure. An adequate history and examination
will usually distinguish these patients, but even if these
factors are missed only 10 per cent of all admissions are
likely to need further investigation based upon the initial
alkaline phosphatase level.

Not all patients with osteomalacia have an elevated
alkaline phosphatase level, and a fasting serum calcium
estimation corrected for albumin (Berry et al. 1973) is an
important adjunct to diagnosis. In the first few days
after admission many of these elderly patients have a
mild degree of renal insufficiency as a consequence of
the circumstances surrounding their fracture or its
subsequent treatment. Under these circumstances the
fasting serum phosphate may be high since it depends
predominantly upon renal function, and thus phosphate
clearance measured as Tmp/GFR (Bijvoet and van der
Sluys Veer 1972) may be a more useful index.

It is the initial level of alkaline phosphatase that
appears to be of the greatest diagnostic significance. The
rise in normal subjects after a fracture is proportionately
greater than in those with osteomalacia whose high
initial values remain relatively unchanged after their
injury. Maximum levels of alkaline phosphatase are
therefore of little discriminatory value. Since this in turn
appears to be the major determinant of the time taken
for normal levels to be achieved, persistent abnormality
in the six to twelve weeks after fracture is of little
significance.

The present study suggests that as the level of
alkaline phosphatase is unaffected by the presence of a
fracture during the first week after injury, it can be used
as a useful screening test for the presence of metabolic
bone disease, provided that liver disease can be ex-
cluded and that the time of the injury is known to within
a few days.

This study would have been impossible without the kind co-operation of the orthopaedic surgeons at the General Hospital, Nottingham. Serum alkaline phosphatase was measured by the Department of Clinical Chemistry, General Hospital, Nottingham, and bone biopsies examined by the University Department of Pathology. This work was performed during the tenure of a Welcome Clinical Research Fellowship.

REFERENCES


