TREATMENT OF BONE WEAKNESS IN PATIENTS WITH FEMORAL NECK FRACTURE BY FLUORIDE, CALCIUM AND VITAMIN D


From the University of Wales College of Medicine, Cardiff

Twenty-three of 46 patients, aged 56 to 95 years, with fracture of the femoral neck (FNF) completed the first trial of 10 months treatment with oral sodium fluoride 60 mg and calcium 1800 mg on alternate days and 1 µg of vitamin D daily. Pre-treatment and post-treatment biopsy specimens and microradiographs of the iliac crest and metacarpal and spinal radiographs were evaluated together with biopsy material from seven untreated age-matched controls with FNF.

In 17 patients the treatment improved the amount and quality of trabecular bone. Cortical thickness increased in nine patients and there were no losses of amount or mineralisation. The treatment was well tolerated by most patients and there were no major side-effects or signs of bone demineralisation. The study also revealed an unexpected rapid post-fracture deterioration of bone tissue in untreated FNF patients; thus there is an increased risk of further fractures which calls for the use of an effective treatment to increase bone mass.

The frequency of femoral neck fractures (FNF) is rising (Zain Elabidien et al. 1984; Boyce and Vessey 1985). The mortality rate is between 12 and 67% at 12 months (Nickens 1983; White, Fisher and Laurin 1987), and the survivors face severe problems and an increasing strain on orthopaedic resources, the treatment in the UK now costing about £165 million per annum (Wallace 1986).

Although FNF is recognised as one of the osteoporotic fractures of old age, efforts to improve osteoporosis by stopping or reversing the bone thinning process have been focused on patients with vertebral fractures. In treatment trials, efficacy has usually been measured by clinical effects rather than by examination of the bone tissue. However, bone biopsies and measurements of the effects of treatment by prospective counts of fractures sustained have become increasingly common (Meunier et al. 1978; Jowsey 1979; Riggs et al. 1980; Briancon and Meunier 1981; Riggs et al. 1982; Meunier et al. 1984; Schnitzler et al. 1987).

Prevention of post-menopausal bone loss by combined hormonal treatment has already met with some success (Hutchinson, Polansky and Feinstein 1979; Weiss et al. 1980) but treatment of established osteopenia in the very old, when FNF is most common, is more difficult. To arrest the progression of osteopenia does not prevent fractures: the process must be reversed and the amount of sound bone tissue increased.

Sodium fluoride in combination with calcium and vitamin D has proved to be potent in stimulating osteoblastic activity and inducing new bone formation (Jowsey et al. 1972; Riggs et al. 1980; Meunier et al. 1984; Vigorita, Lane and Schwartz 1984). Since the first reports of dense bones in areas with natural fluorosis (Singh et al. 1963) and of the introduction of fluoride in clinical studies (Rich and Ensinck 1961; Rich, Ensinck and Ivanovich 1964), results of some of the early trials, with fluoride alone, expressed concern over the osteomalacic character of the new fluoride-induced bone. Subsequent trials have established, however, that when calcium and vitamin D are given in sufficient doses together with fluoride, the induced bone is adequately mineralised (Jowsey et al. 1972; Riggs et al. 1980; Riggs et al. 1982). The repeated claims of increased bone mass certainly justify such treatment in FNF. The formation
of fluoride-stimulated cancellous bone might also prevent further fractures, influence the consolidation of the present fracture and facilitate the revascularisation and rebuilding of the avascular femoral head.

For a bone-mass-increasing treatment to prove effective diagnosis of the underlying cause of the bone weakness must first be established. Patients with "osteoporotic" FNF could have not only thinning of the bone tissue but also changes in trabecular architecture (Arnold 1981; Parfitt et al. 1983), an increase in the amount of osteoid (Chalmers et al. 1969; Aaron et al. 1974) and structural deterioration of the bone matrix and mineral (Ralis 1983 a,b). These changes can be determined only from bone biopsy; this also permits other pathological conditions to be established and the effect of treatment to be monitored (Aaron et al. 1974; Jowsey 1977; Ralis et al. 1984). In this study only those FNF patients with both pre-treatment and post-treatment bone biopsies are presented. The aim was to assess if combined fluoride treatment would increase their bone mass.

PATIENTS AND METHODS

Initially, 86 patients who were admitted to the Cardiff Royal Infirmary with FNF were selected because their iliac crest biopsy results excluded pathological conditions that would further aggravate bone weakness – e.g., Paget's disease, myeloma, renal osteodystrophy, secondary hyperparathyroidism. Of these, 46 were able to attend the monthly clinic and started treatment. Before the end of the trial, 23 died, could not attend, or refused the second biopsy. Thus 23 patients completed the study. All were women, aged 56 to 95 years (mean 71.04 years, s.e.m. 2.78), and nine of them had had a subcapital fracture. Seven untreated FNF patients were controls, aged 68 to 84 years (mean 77.29, s.e.m. 2.24).

Treatment and follow-up. Patients were given for 10 months 60 mg sodium fluoride in gelatinised capsules on alternate days (in three 20 mg doses), 1800 mg calcium carbonate on alternate days (as three Sando-Calc 600 mg tablets) and 1 μg of vitamin D₃, 1-alphahydroxy-cholecalciferol in capsule form. To prevent the production of insoluble calcium fluoride the patients were warned not to take sodium fluoride and calcium carbonate on the same day. During follow-up the patient's clinical status, progress of the fracture healing and blood serum biochemistry values (calcium, phosphate and alkaline phosphatase) were assessed at two to three monthly intervals. The number of vertebral collapses before and after treatment was counted on radiographs of the dorsal and lumbar spine. Second and fourth metacarpal cortical indices (Barnett and Nordin 1960) were measured on radiographs of the non-dominant hand.

Bone samples. In osteoporosis treatment trials bone biopsy has been accepted as an essential routine procedure (Meunier et al. 1978; Jowsey 1979; Duncan, Rao and Parfitt 1980; Riggs et al. 1980; Arnold 1981; Ralis 1983a), and we obtained the approval of the ethical committees of the Regional Medical and Surgical Divisions. At operation a trans-iliac bone biopsy was taken with an 8 mm RNOH-trephine from an ipsilateral site 2 cm behind the anterior superior spine and 2 cm below the iliac crest. The second biopsy (after treatment) was taken under local anaesthetic, at the identical contralateral site. After fixation in 10% buffered formalin half the specimen was decalcified and paraffin embedded sections were either stained by haematoxylin and eosin and Ralis' tetrachrome (Ralis and Ralis 1975) or kept unstained for autofluorescence. From the other half of the specimen, undecalcified resin-embedded sections were cut on a Jung heavy duty microtome and stained by haematoxylin and eosin, Goldner's Trichrome and Von Kossa's methods. Sections 60 to 90 μm thick were also cut for microradiography on Softex apparatus and for several specimens a thin slab was retained for scanning electron microscopy (Jeol scanning electron microscope with a 40 kV accelerating potential) of ion-etched specimens (Ralis and Turner 1981).

Measurements were done with a semi-automatic image analyser (Kontron MOP-Videoplan with JVC-TV camera). The trabecular bone volume (TBV), trabecular thickness (TT), osteoid surface extent and area and the cortical bone thickness (CT) were measured in both paraffin and undecalcified sections to minimise the sampling errors; results were expressed as mean values. Trabecular bone measurements were done separately in the two subcortical areas and in the mid-core of the biopsy specimen and were expressed as their proportional ratios. TT and CT were measured at regular
intervals in a direction perpendicular to their long axis. The amount and surface extent of the osteoid tissue, identifiable both in paraffin tetrachrome and undecalcified sections, were assessed to detect histological osteomalacia; if there was any doubt that the osteoid area might exceed 4% of the TBV, the amount was quantified.

Bone mineral distribution and density were evaluated in slab microradiographs semi-quantitatively (minimum, moderate or sharp density increase or decrease) by two independent observers before and after treatment to detect any irregularities or abnormal features.

RESULTS
The drugs were, in general, well tolerated. There were six patients with mild or moderate gastric irritation at the beginning of the trial when sugar-coated sodium fluoride tablets were used, but these effects stopped when the tablets were replaced by gelatinised capsules. There were no complaints about periarticular or plantar fascial pains or renal, hepatic or other complications.

In all the FNF patients before treatment serum biochemical values were within normal limits (calcium 2.25 to 2.60 mmol/l, phosphate 0.8 to 1.4 mmol/l and alkaline phosphatase 30 to 90 iu/l), with about half the values in the lower range of normal. After treatment most patients showed no substantial change in these values, apart from two – both treatment responders – whose values rose to the upper range of normal. Metacarpal cortical indices did not change significantly. The initial values for the second metacarpal index (2MCI) were between 41.3 and 68.7, and were in most cases age-related. After treatment the 2MCI dropped in one patient by 2.5% and in two, both responders, it increased by 3%. Post-treatment radiographs of the dorsal and lumbar spine showed no changes in the bone density or shape of the vertebral bodies, or increase in the number of compression fractures; there were no fractures of other bones. In the control group two new vertebral fractures occurred.

Bone biopsy
Pre-treatment values and controls. TBV values at the time of fracture varied, with age, between 8.8 and 17.8%. In patients over age 65 to 70 TBV did not significantly differ from that of the normal ageing population (Gallagher et al. 1972; Nordin 1973; Ralis 1983a,b), which confirms doubts about bone thinning being the sole cause of FNF. Mean values for TT were between 0.05 and 0.12 mm and for CT were between 0.22 and 0.86 mm.

In a normal population after the menopause TBV declines annually by about 1.2 to 2.2% and after the age of 65 by about 0.8 to 1.3% (Gallagher et al. 1972; Ralis 1983a; Dambacher, Ittner and Ruegsegger 1984). However, in our untreated control patients during the 12 to 18 months after fracture the average TBV loss was 27% (s.e.m. 13.7), with 15.5% (s.e.m. 12.5) loss of TT, and 51.7% (s.e.m. 12.4) loss of CT.

Values after treatment. Our treated patients were classed as non-responders – those who showed a post-treatment decline in the mean bone mass similar to that of the controls; responders – those who either retained values similar to pre-treatment values (since the bone loss seen in controls did not occur) or who showed a moderate gain; and high responders – those who had a substantial gain in TBV (at least 2 s.d. higher than the pre-treatment value) (Fig. 1). The mean TT and mean CT were similarly adjusted for the post-fracture loss in the controls.

Trabecular bone volume. Seventeen of the 23 patients responded to treatment with an average TBV gain of over 80%; six of these 17 were high responders – their TBV increased on average by over 160% (p<0.02;

### Table 1. Response to treatment and gain in bone in 23 treated patients compared with untreated controls

<table>
<thead>
<tr>
<th></th>
<th>Mean trabecular bone volume</th>
<th>Mean trabecular thickness</th>
<th>Mean cortical thickness</th>
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</thead>
<tbody>
<tr>
<td><strong>Controls with FNF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean loss (per cent)*</td>
<td>-27</td>
<td>-15.5</td>
<td>-51.7</td>
</tr>
<tr>
<td><strong>All treated patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean gain (per cent)†</td>
<td>+64.4</td>
<td>+40.7</td>
<td>+37.7</td>
</tr>
<tr>
<td><strong>Non-responders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (per cent) of patients</td>
<td>6 (26.1)</td>
<td>9 (39.1)</td>
<td>14 (60.9)</td>
</tr>
<tr>
<td>Mean gain (per cent)†</td>
<td>+6.7</td>
<td>+1.1</td>
<td>+3.2</td>
</tr>
<tr>
<td><strong>Responders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (per cent) of patients</td>
<td>11 (47.8)</td>
<td>5 (21.8)</td>
<td>6 (26.1)</td>
</tr>
<tr>
<td>Mean gain (per cent)†</td>
<td>+42.9</td>
<td>+29.8</td>
<td>+56.6</td>
</tr>
<tr>
<td><strong>High responders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (per cent) of patients</td>
<td>6 (26.1)</td>
<td>9 (39.1)</td>
<td>3 (13.0)</td>
</tr>
<tr>
<td>Mean gain (per cent)†</td>
<td>+161.0</td>
<td>+73.3</td>
<td>+198.0</td>
</tr>
</tbody>
</table>

* after 10 to 18 months with no treatment
† compared with controls
Tables I and II). Age and type of fracture seem to determine the responsivenes to treatment: the mean TBV increase in patients aged under 70 was 83% compared with 67% in those aged 71 or more and more patients with a subcapital fracture responded to treatment than those with trochanteric fractures (79% and 54% respectively), although neither difference was significant.

**Mean trabecular thickness.** Changes in TT are related to changes in TBV and in most cases the values were similar. The TT was monitored, however, to elucidate whether the increase in TBV during fluoride treatment is due to the increase in the amount of bone of the existing trabeculae, or the formation of new trabeculae and structural units. If the TBV increased but the mean TT did not, then we can assume that the bone volume has increased because the number of trabeculae has risen. In all samples the gains in TBV and TT were compared and it seems that in at least seven of the 23 treated patients the TBV increased as a result of the formation of new trabeculae and units (Fig. 2).

**Mean cortical thickness.** Table I shows that in 14 patients the cortical bone did not react significantly to treatment; however, there were no losers. In nine patients it increased.

**Osteoid tissue.** In none of the pre-treatment biopsy specimens did the amount of osteoid tissue exceed 4% of the TBV, and after treatment this remained unchanged in most. In eight patients the seams became narrower and covered a smaller proportion of the bone surface but in the two with an usually high response to treatment (TBV gains of over 265% and 371%, respectively) the outer, most newly formed margins of the grossly enlarged trabeculae were clearly hypomineralised. However, this tissue was lamellar, slowly and insufficiently mineralised bone and not a mineral-free osteoid (Fig. 2). Such tissue has been described before in osteomalacia as under-mineralised osteoid bone (Ralis and Ralis, 1978).

**Bone mineral density.** In 14 of 21 treated patients (excluding the two high responders), post-treatment microradiographs showed greater mineralisation of the trabecular and cortical tissue components than was present before treatment and there were no areas of decreased mineral density. In the two patients with post-fluoride bone over-production the borders of cortical cavities and trabecular surfaces showed low mineralisation, thus identifying the presence of under-mineralised osteoid bone.

**DISCUSSION**

The low incidence of side-effects in this trial accords with other studies reporting low toxicity of fluoride when used in moderate doses and in combination with vitamin D and calcium (Schäffer et al. 1978; Delmas et al. 1984; Meunier et al. 1984). We used one of the lowest doses of sodium fluoride (30 mg daily) reported and this, together with the division of the dose into three portions probably contributed to the good tolerance. Side effects such as periarticular and plantar fascial pains or osteomalacia and trabecular bone stress fractures (Schäffer, 1978; Dambacher et al. 1984; Schnitzler 1984) have been recorded with higher doses and more frequent administration of the drug or with treatment by sodium fluoride alone. The normal values for serum calcium, phosphate and alkaline phosphatase before and after treatment accord with the findings of other workers (Faccini, Exton-Smith and Boyd 1976; Briancon and Meunier 1981; Meunier et al. 1984). Our findings of no further spinal fractures in the treatment group and two new fractures in the control group are similar to those of other observers (Jowsey et al. 1972; Jowsey 1979; Riggs et al. 1980; Briancon and Meunier 1981; Riggs et al. 1982; Schnitzler et al. 1987). The decrease in the rate of vertebral fractures in the treatment group probably implies improvement of the cancellous bone in the proximal femur.

The rapid deterioration in the amount of trabecular and cortical bone seen in our controls indicates a poor prognosis for the untreated FNF patient. Unless there is a rapid return of the patient’s mobility (exercise and mobility are recognised as effective ways of slowing down disuse osteopenia) or the bone mass is improved by effective therapy, further bone deterioration lowers the fracture threshold and increases mortality. This is also important because only patients with the same fracture and similar circumstances of postoperative hospitalisation and mobility should be used as untreated controls when assessing the efficacy of treatment trials.

Our results show that the FNF patients reacted very well to the combined fluoride therapy (Fig. 3). The
average increase in TBV was in the upper range of values for this treatment and for treatment with other drugs used in osteoporosis. Since an increase in the amount of bone tissue improves the mechanical strength of bone (Dalén, Hellström and Jacobson 1976; Briancon and Meunier 1981) and compressive bone strength increases after combined fluoride therapy (Baud et al. 1983) this treatment is likely to strengthen the fracture-prone bone tissue in the ageing proximal femur.

The proportion (about a quarter) of our patients not responding to treatment is much the same as that reported in other fluoride trials. This lack of response could be due to poor patient compliance, to metabolic blocking in transfer of the drug to bone tissue, or to the unresponsiveness of osteoid and bone-building cells. The identification of good or poor responders would be important in the selection of patients for treatment, but requires further study.

The slow response of cortical bone to treatment was expected; it illustrates the differences between trabecular and cortical bone components. However, if the treatment had been continued for two or three years, as some workers advocate (Dambacher et al. 1978; Meunier et al. 1978; Meunier et al. 1984), the cortical bone response might have been more like that of the cancellous bone. The fact that we had no cortical bone losers (i.e., none had lost more than the controls) and that TBV responders were also cortical-bone responders shows that an increase of trabecular bone mass by fluoride is not necessarily accompanied by loss of amount of cortical bone or of its mineral content. Yet this loss might occur if the simultaneous intake of calcium was insufficient.

The findings of only a small (below 4%) TBV of osteoid in pre-treatment biopsy material lends support to the view that histological osteomalacia does not play a

Table II. Gain in the amount of trabecular and cortical bone in all 23 treated patients and in responders to treatment

<table>
<thead>
<tr>
<th></th>
<th>Mean trabecular bone volume</th>
<th>Mean trabecular thickness</th>
<th>Mean cortical thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FNF controls</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean gain (s.e.m.)</td>
<td>0 (13.7)</td>
<td>0 (12.5)</td>
<td>0.29 (12.4)</td>
</tr>
<tr>
<td><strong>All treated patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean gain (s.e.m.)</td>
<td>64.4 (20.0)</td>
<td>40.7 (9.8)</td>
<td>37.7 (15.5)</td>
</tr>
<tr>
<td>Significance*</td>
<td>p &lt; 0.1</td>
<td>p &lt; 0.5</td>
<td>p &lt; 0.5</td>
</tr>
<tr>
<td><strong>Responders to treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number (per cent) of patients</td>
<td>17 (73.9)</td>
<td>14 (60.9)</td>
<td>9 (39.1)</td>
</tr>
<tr>
<td>s.e.m.</td>
<td>10.1</td>
<td>10.8</td>
<td>11.3</td>
</tr>
<tr>
<td>Mean gain (s.e.m.)</td>
<td>84.6 (26.1)</td>
<td>57.8 (10.1)</td>
<td>103.7 (31.9)</td>
</tr>
<tr>
<td>Significance*</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.05</td>
<td>p &lt; 0.02</td>
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</tbody>
</table>

* versus controls
substantial part in the aetiology of FNF (Hodkinson 1974; Evans, Ashwell and Dunstan 1981; Wicks et al. 1982; Ralis et al. 1985). With respect to post-fluoride osteoid production, with two exceptions, there were no signs of post-fluoride osteomalacia, mottled bone or bone demineralisation. Such changes seem to occur mainly after administration of fluoride in high doses or without calcium (Olah, Reutter and Dambacher 1978; Schaffer et al. 1978; Vigourita and Suda 1983; Meunier et al. 1984). The two patients with exceptionally high TGV gains illustrate the importance of a simultaneous and adequate supply of calcium in fluoride therapy – the fluoride-induced bone was produced so fast that even 1800 mg of calcium on alternate days was insufficient to mineralise it all.

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