We investigated the effect of calcitonin in the prevention of acute bone loss after a pertrochanteric fracture and its ability to reduce the incidence of further fractures in the same patient.

Fifty women aged between 70 and 80 years who had a pertrochanteric fracture of the hip were randomly allocated to group A (200 IU of nasal salmon calcitonin daily for three months) or group B (placebo).

Patients in group A showed a significantly higher level of total alkaline phosphatase and osteocalcin on the 15th day after injury and a significantly higher level of bone alkaline phosphatase on the 90th day after surgery. These patients also had significantly lower levels of urinary C-telopeptide (CrossLaps) on the 15th, 45th and 90th days after injury and lower levels of urinary hydroxyproline on the 15th and 45th days after injury. Patients in group A had significantly higher bone mineral density at all recorded sites except the greater trochanter at three months and one year after operation. After a four-year period of clinical observation, five patients (24%) in group B sustained a new fracture, in four of whom (20%) it was of the contralateral hip.

Our findings show that calcitonin reduces acute bone loss in patients with pertrochanteric fractures and may prevent the occurrence of new fractures of the contralateral hip in the elderly.
in patients who had sustained pertrochanteric fractures of the hip.

Patients and Methods
All female patients aged between 70 and 90 years who had sustained a pertrochanteric fracture of the hip and who had been admitted to our Orthopaedic Department for surgery were included in the study. The exclusion criteria were: 1) a previously diagnosed and treated bone metabolic disease; 2) the use of any medication which interfered with bone turnover; 3) a previous hip or vertebral fracture; 4) inability to walk outside the home; 5) an inability to understand or co-operate; 6) the presence of abnormal initial clinical and laboratory screening tests; and 7) alcohol abuse and heavy smoking (over 20 cigarettes per day).

All patients who were entered into the trial underwent radiography of the lumbar spine and the contralateral hip on the day of admission in order to exclude disorders which would make measurements of bone mineral density (BMD) at these sites unreliable. Measurements of the levels of 25-Vitamin D3, intact parathyroid hormone (PTH) and thyroid stimulating hormone (TSH) were also taken in order to exclude serious endocrine disorders which might affect bone metabolism.

The study was a randomised, placebo-controlled trial. Written informed consent forms were obtained from all patients and the study was approved by the National Ethical Committee. Fifty patients were included in the study over a period of four months, and were randomly allocated into two groups using sealed envelopes which were opened on the day after admission. The patients were followed up for four years (Fig. 1). Both groups were comparable in age, body-weight, height and the site of fracture (Table I). For the 25 patients in group A, a nasal spray of 200 IU of salmon calcitonin was used daily for three months. For the 25 patients in group B a placebo spray was used in a similar way. Administration of the nasal calcitonin or placebo began on the day after admission.

Serum and urine samples were collected in the morning, after an overnight fast and abstinence from tobacco, on the 1st, 7th, 15th, 45th and 90th days after injury from all the patients. The urine samples were collected as the second void, two hours into the morning. All samples were assayed at the end of the study in order to reduce interassay variability and were stored at -20°C until they were analysed. The biochemical markers of bone formation were osteocalcin (Roche Diagnostics, Mannheim, Germany), total alkaline phosphatase (Roche Diagnostics), and the specific bone alkaline phosphatase (ELISA; Metra Biosystems, Mountain View, California). The biochemical markers of bone resorption were urinary type-1 C-telopeptide breakdown products (uCTX) (CrossLaps ELISA; Osteometer Biotach A/S, Herlev, Denmark) and urinary hydroxyproline (Hyprognosticon, Organon Teknika Boxtel, The Netherlands). Bone alkaline phosphatase was only analysed on the first and 90th days after injury.

The BMD was measured in all patients using dual energy x-ray absorptiometry (Lunar Corp, Madison, Wisconsin) at standardised positions of the lumbar spine in the frontal plane and of the contralateral hip. The BMD at L1/L4, the neck of the femur, the greater trochanter and at Ward’s triangle were assessed. All measurements were performed on the fourth post-operative day, on the 90th day and one year after the fracture. The stability of the measurements was controlled by scanning a phantom of known BMD every three months throughout the study. Measurements were reproducible with a coefficient of variation of less than 2%,
which confirmed previously published studies. The short-term precision error of the BMD studies in vivo was also estimated in five patients for whom three separate measurements were made on the same day after repositioning. The precision error was 1.5%.

**Statistical analysis.** Statistical analysis of the data which were derived from the measurement of the biochemical bone markers was performed with using ANOVA, adjusted for age, by estimation of the mean percentage variation from the initial baseline value. The BMD values of the lumbar spine and hip and the osteocalcin levels were analysed using the Mann-Whitney test. Comparisons were made between the mean percentage variation and the initial baseline value.

**Results**

All patients underwent surgery within three days of sustaining their fractures and were mobilised out of bed on the second day after operation. Partial weight-bearing was started on the third day and full weight-bearing was allowed at the end of the second week. All received prophylactic antibiotics and low-molecular-weight heparin. There were no side-effects from the calcitonin or placebo treatment and no voluntary interruptions of treatment. No post-
operative complications which might interfere with bone metabolism and rehabilitation were recorded.

**Bone formation markers.** The change in the values of total alkaline phosphatase for both groups is shown in Figure 2. Patients in group A (calcitonin-treated) showed significantly higher values \((p < 0.005)\) by the 15th day after injury. They also showed significantly higher \((p < 0.002)\) values for bone alkaline phosphatase by the 90th day after injury (Fig. 3). The change in the serum osteocalcin for both groups is shown in Figure 4. Group A patients showed significantly higher values \((p < 0.05)\) by the 15th day after injury.

**Bone resorption markers.** Values for urinary hydroxyproline (urinary creatinine ratios) and C-telopeptide (CrossLaps) for both groups are shown in Figures 5 and 6. Patients in group A had a significantly lower excretion of
hydroxyproline on the 15th (p < 0.015) and 45th (p < 0.05) days after injury (Fig. 5). Significantly lower values of CrossLaps were observed in group A on the 15th (p < 0.045) and 45th (p < 0.002) days after injury (Fig. 6).

**Lumbar spine BMD.** The change in BMD in the lumbar spine for both groups is shown in Figure 7. When the changes were compared between the two groups, group A was found to have a significantly higher level both at three months (p < 0.03) and at the end of one year (p < 0.002).

**Contralateral (intact) hip BMD.** The change in the BMD of the contralateral hip (neck, trochanter and Ward’s triangle)\(^\text{20}\) for both groups is shown in Figures 8 to 10 respectively. Group A had significantly higher values for the BMD in the region of the neck of the contralateral hip than group B at three months (p < 0.005) and at one year (p < 0.005) (Fig. 8). Within each group there was also a significant change in BMD in the neck of the femur at three and 12 months after surgery (group A, p < 0.05 at three months, p < 0.0005 at 12 months; group B, p < 0.0005 at three and 12 months). In the trochanteric region, no significant difference was found between the groups at either time interval (Fig. 9). Within group A there was no significant difference between the baseline values and those at three months although this difference became significant (p < 0.005) by 12 months. For group B these differences were significant at three (p < 0.01) and 12 (p < 0.0005) months. In the region of Ward’s triangle, group A had a significantly higher BMD than group B at
both three months (p < 0.01) and at one year (p < 0.01) after surgery (Fig. 10). Group A showed no significant change from the baseline values at either three or 12 months after operation. Group B did show a significant difference on both occasions (three months, p < 0.005; 12 months, p < 0.002).

Incidence of new fractures. At the end of the four-year period of clinical observation, five patients in group B (5/21, 24%) had sustained a fresh fracture, in the contra-lateral hip (three pertrochanteric and one cervical) in four, and of the distal end of the radius in one. In group A, only one patient sustained a new hip fracture (1/22, 4.6%). This patient also fractured two ribs after a fall. The mean interval between the first and second hip fractures was 18 months (15 to 21). No patient sustained a vertebral fracture during the observation period.

Discussion
Trauma, prolonged bed rest and inactivity can cause the clinical syndrome of immobilisation or disuse osteoporosis. Acute therapeutic immobilisation results in a mean bone loss of 1% per week, or more than 30% in six months, as compared with age-related physiological bone loss of 1% per year. It has been shown in histomorphometric studies that immobilisation bone loss is caused by a combination of increased resorption and decreased rate of formation of bone. An uncoupling...
between formation and resorption takes place. It has been suggested that the coexisting bone-collagen breakdown is not a self-limiting process in immobilised patients, and that a new equilibrium cannot be reached in the skeleton.24-26 Young individuals can slowly restore bone loss induced by disuse, a process which can take up to 36 weeks.27,28 With the restoration of functional activities, an almost total reversal of bone loss can be observed in the young, while in the elderly a considerable residual deficiency of bone mass can be expected.18,28

Despite the clinical importance of fractures of the hip in the elderly, few studies have been performed to assess the bone turnover for this age group. It has been suggested that elderly patients have an increased bone turnover because of secondary hyperparathyroidism.25,29 Levels of serum osteocalcin and urinary hydroxyproline have been reported to be either low or normal.30-33 However, co-existing acute changes in body fluids, and perhaps of bone turnover, related to the recent trauma, may obscure subtle changes in bone remodelling. Akesson et al18 found statistically significant increase of urinary CrossLinks excretion when patients with hip fractures were compared to age-matched, elderly, healthy subjects. They concluded that increased bone resorption may be a determinant of the low bone mass which characterises patients with fractures of the hip and that these abnormalities apparently precede the fracture. We have also shown that patients with such fractures have an increased bone turnover for up to 15 days after their operation.18 These findings are supported by a more prospective study in which baseline measurements of urinary C-telopeptide (CrossLaps) excretion of free deoxypyridinoline in elderly patients with fractures of the hip, were higher than in a control group without a fracture.35

Calcitonin can be used to prevent fractures of the hip in elderly patients and may also modify abnormalities of bone turnover in these patients.1,12,17 Different methods of administration have been used. Rectal calcitonin has been employed for the prevention of bone loss in the elderly,36 but Kollerup et al37 did not observe any significant effect of calcitonin suppositories on bone metabolism in established osteoporosis. In a short study it has been shown that the parenteral administration of 100 IU of calcitonin per day for two weeks can prevent bone loss during the immediate post-operative period in patients with a fracture of the hip especially those who cannot be mobilised immediately.18 Moreover, the intranasal administration of 200 IU of salmon calcitonin per day can counteract the early increase in bone resorption which is seen during short-term immobilisation for reasons other than fracture.18

In our study, the intranasal administration of 200 IU of calcitonin per day for three months after injury was used in patients who had sustained a pertrochanteric hip fracture. This was an attempt to investigate thoroughly the effect on bone turnover. Changes were assessed by evaluating specific biochemical bone markers and measurements of the BMD at different skeletal sites. The biochemical markers used in our study are sensitive and specific non-invasive indices of bone turnover. In combination with studies on the BMD they can predict the risk of future fracture in post-menopausal women.30,31,38-42 Moreover, studies on the BMD are the most accurate way of monitoring both the therapeutic effect and the risk of fracture in metabolic bone diseases.1

Values for bone alkaline phosphatase and osteocalcin, which are the more sensitive and specific markers of bone formation,30,40 were found to be significantly higher in the calcitonin-treated group on the 15th post-operative day and remained high throughout the three-month observation period. This may reflect a long-term influence on bone osteoblastic activity which may improve the speed of bone healing. Values for total bone alkaline phosphatase were also significantly increased in the calcitonin-treated group at three months. In our previous short-term study, a significant change in the values of total bone alkaline phosphatase was not found in the first two weeks after fracture of a hip.18 However, this marker represents a biochemical index of bone formation of relatively low sensitivity and specificity.43 Urinary hydroxyproline and CrossLaps values, which are more sensitive and specific markers of bone resorption,38,39,44-46 were significantly lower in the calcitonin-treated group at both the 15th and 45th days after surgery. This confirms our earlier findings and shows that intranasal calcitonin inhibits urinary hydroxyproline and CrossLaps excretion in patients with acute immobilisation after a fracture of the hip.

In our present study the calcitonin group had an increase in values of BMD of the lumbar spine and the contralateral femoral neck up to the third month of observation. Moreover, the reduction in BMD in the greater trochanter and Ward’s triangle in the calcitonin-treated group was less than for the placebo group during the same period. After the third post-operative month, all the BMD values showed a parallel reduction for both groups. It appears that the intranasal administration of calcitonin after a recent pertrochanteric fracture of the hip protects against bone loss for at least three months. It has also been recently reported that an accelerated loss of bone mineral takes place after a fracture of the hip and the mean value of that loss one year later may reach 2.4% in the lumbar spine and 5.4% in the contralateral femoral neck.47 In our study the change in the mean BMD for group A, from its initial baseline value in the contralateral, healthy, femoral neck, one year after the fracture, was +3.63% but -2.04% in the lumbar spine. Although different methods of statistical analysis do not allow us to compare these findings directly, the increase in the BMD of the femoral neck suggests that calcitonin is effective in preventing bone loss after fracture of a hip even when it is no longer being taken.

In our study, a considerable reduction in BMD was found at different skeletal sites for up to three months after operation. This significant reduction may explain the high incidence of future fractures in the contralateral hip.
Nakamura et al,\(^4\) in an effort to determine the precise role of proximal femoral fragility in the development of a fracture of the hip, also showed that patients with per trochanteric fractures had a lower BMD in the contralateral hip when compared with a healthy control group A. A similar reduction in bone mass has been reported in studies which have used shorter periods of observation.\(^1,16,18,49-52\)

In our study the incidence of new fractures in the placebo-treated group was 20\%, a figure which is similar to that of Schroder et al.\(^8\) Calcitonin prevented a loss in bone mass and no patient developed a new trochanteric fracture within the four-year period of observation. This suggests that the calcitonin can prevent architectural changes in the proximal femur which predispose to new fractures.

A trochanteric fracture of the hip in the elderly causes both a considerable change in bone turnover and a large reduction in the bone mass in both the lumbar spine and the contralateral, healthy hip. Orthopaedic surgeons, often ignore these changes and their long-term consequences and focus solely on the techniques of fixation. The intranasal administration of 200 IU of calcitonin decreases bone resorption, influences bone formation and reverses the loss in bone mass in the lumbar spine and the contralateral hip. It may also prevent the occurrence of a new fracture of the hip in the elderly.

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References


