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OSTEOMALACIA IN FRACTURES OF THE PROXIMAL FEMUR

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The occurrence of osteomalacia was studied in 58 hip fracture patients who were admitted to the University Central Hospital of Kuopio for operative treatment. Findings indicating osteomalacia were frequent in the series. Hypocalcaemia was found in 70 per cent and an increase in serum alkaline phosphatase in 22 per cent of the patients. Urinary calcium excretion was decreased in 45 per cent and urinary hydroxyproline excretion was increased in 70 per cent of the cases. The serum levels of 25-hydroxyvitamin D and 24,25-dihydroxyvitamin D were significantly decreased in the patients compared with the controls. Histomorphometric analysis revealed no difference in the amount of trabecular bone in the patients compared with the controls, but the amount of osteoid and resorption surfaces was increased in the patients. Histological osteomalacia was found in 12 out of 50 patients (24 per cent). In 10 of these 12 cases the diagnosis of osteomalacia was supported by biochemical changes.

There was only one patient, a 29-year-old man with glutein enteropathy who had an evident reason for osteomalacia. The most obvious cause of osteomalacia was the lack of vitamin D due to a deficient diet and lack of exposure to sunlight.

The conclusion drawn was that osteoporosis was the main cause and osteomalacia was an important aggravating factor in the bone fragility in these hip fracture patients.

Key words: hip fracture; osteoporosis; osteomalacia; vitamin D

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The frequency of fractures of the proximal femur increases with age (Alffram 1964, Bauer 1960, Knowelden et al. 1964 and femoral fractures are more common in women than in men (Alffram 1964, Chalmers et al. 1967, Knowelden et al. 1964). Osteoporosis is the main reason for the bone fragility in hip fractures (Alffram 1964, Bauer 1960, Menczel et al. 1976, Stevens et al. 1962) and hence, due to the decreased strength of bone, minor violence can cause fractures, especially in old age. Osteomalacia has also been found to be common in femoral fracture cases (Aaron et al. 1974, Chalmers et al. 1969, Daw et al. 1979, Jenkins et al. 1973, O'Driscoll 1973) and it often co-exists with osteoporosis (Aaron et al. 1974, Chalmers 1968, Gallagher et al. 1972). Impairment of the metabolism and subnormal serum levels of vitamin D may be one reason for the fragility of bones in femoral fracture patients (Baker et al. 1979, Brown et al. 1976, Daw et al. 1979, Weisman et al. 1978). There is a marked seasonal variation in the serum levels of 25-hydroxycholecalciferol (Brown et al. 1976, Savolainen et al. 1980), but it probably is not important in the pathogenesis of femoral fractures. There is some evidence that also femoral fractures have a seasonal variation (O'Driscoll 1973), but this is probably due to environmental factors, for example slippery conditions in wintertime.

The purpose of this study was to evaluate the frequency of osteomalacia in patients with a

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femoral neck fracture, using biochemical tests and histomorphometric analysis of the iliac crest cancellous bone.

PATIENTS AND METHODS

Fifty-eight hip fracture patients, 42 women with a mean age of 76 years (range 53–91) and 16 men with a mean age of 71 (range 29–91), who were admitted to the University Central Hospital of Kuopio between September 1978 and July 1979 for operative treatment were included in the study. Moribund patients were not operated on and were thus excluded from the study. Forty-four per cent of the female and 31 per cent of the male patients were living in an institution for the elderly when they suffered the fracture. Two female patients had undergone gastric resection according to Billroth II 9 and 33 years earlier. Two women were having long-term cortisone therapy for rheumatoid arthritis. One of the male patients was an alcoholic. Twenty-nine of the fractures were medial and 29 were lateral. Heat-stable serum alkaline phosphatase was normal in every patient. All but an 81-year-old woman with a slightly increased serum creatinine (S-crea 143 μmol/l) had a normal serum creatinine level. Forty-four per cent of the females and 38 per cent of the males had hypoproteinaemia and 20 per cent of the females and 13 per cent of the males had hypoalbuminaemia. Twenty-seven per cent of the women and 40 per cent of the men were anaemic.

Serum calcium (S-Ca, normal range 2.30–2.75 mmol/l), inorganic phosphate (S-Pi, normal range 0.81–1.45 mmol/l), alkaline phosphatase (S-ALP, normal range in females 50–200 IU/l and in males 60–250 IU/l), diurnal hydroxyproline excretion (dU-HOP, normal range 22–65 years: 65–180 $\mu mol/m^2$ and over 65 years: 50–150 $\mu mol/m^2$) and diurnal calcium excretion (dU-Ca, normal range 1.3–7.3 mmol) were determined by routine laboratory methods. S-Ca values were corrected to serum albumin values.

Total serum 25-hydroxyvitamin D (S-25OHD, nmol/l) and serum 24,25-dihydroxyvitamin D (S-24,25$(OH)_2$D, nmol/l) were determined. The assay involved methanol/chloroform extraction of serum lipids followed by separation of the mono- and dihydroxyvitamin D metabolites and purification from interfering contaminants by chromatography on Sephadex LH-20 and by high-performance liquid chromatography (HPLC) (Parviainen et al. 1981, Savolainen et al. 1980). 25OHD was quantified by HPLC using UV detection and 24,25$(OH)_2$D with a competitive protein binding assay using human or rat serum binding protein. Age- and sex-matched control values were obtained from healthy persons who were matched also according to season so that equal proportions of summer and winter values of vitamin D existed in the patient and control groups.

The histomorphometric values of biopsy specimens from the iliac crest cancellous bone were determined from 36 women and 14 men. Bone biopsies, 5 mm in diameter and 2 cm in length, were taken with a trephine 2 cm behind the anterior superior iliac spine. Five micron thick methacrylate embedded undecalcified bone sections were cut using a motor driven Jung K microtome equipped with HK knives. The bone sections were stained with Masson-Goldner trichrome stain. The histomorphometric analysis was performed according to Merz & Schenk (1970a, b). The volumetric density of cancellous bone (V_v, per cent), percentage of trabecular bone volume occupied by osteoid (V_{vo}, per cent), trabecular bone surface covered with osteoid (OS, per cent) and trabecular resorption surfaces (RS, per cent) were determined. Age- and sex-matched controls were obtained from a control material collected from autopsy cases that had not had any disease or medication that might influence bone mineral metabolism (Hoikka & Arnala 1981).

Mann-Whitney's U-test was used in the statistical analysis.

RESULTS

The abnormal biochemical findings are presented in Table 1. Hypocalcaemia was found in 70 per cent and an increase in serum alkaline phosphatase in 22 per cent of the patients. Seventy per cent of the cases had an increase in dU-HOP and 45 per cent had a decrease in dU-Ca. The serum concentrations of 25OHD and 24,25$(OH)_2$D were significantly lower in the patients with a femoral neck fracture than in age- and sex-matched healthy controls (Table 2). In the histomorphometric study of the iliac crest cancellous bone, no difference was found in V_v between the patients and the age- and sex-matched controls (Table 3), but V_v was less than 10 per cent, suggesting severe osteoporosis in 13 out of 36 females and in one out of 14 males. V_{vo}, OS and RS were statistically significantly increased in the patients compared with the controls (Table 3). V_{vo} of over 3.4 per cent (normal mean + 2 SD) was found in six out of 36 females (17 per cent) and in six out of 14 males (43 per cent). Three women with a V_v of less than 10 per cent had an increase in V_{vo}. Nine of the 12 cases with an increase in V_{vo} had a lateral femoral neck fracture and three had a medial fracture. No

Table 1. Abnormal biochemical values in femoral neck fracture patients

Test	Laboratory findings Females N	%	Males N	%
S-Ca↓	27/40	68	12/16	75
S-Pi↓	3/34	9	2/14	14
S-ALP↑	9/39	23	3/16	19
dU-HOP↑	29/41	71	11/16	69
dU-Ca↓	21/40	53	4/16	25
S-Ca↓ + S-ALP↑	6/37	16	1/16	6
S-ALP↑ + (S-Ca↓ and/or dU-Ca↓)	8/37	22	2/16	13

Table 2. Serum concentrations (mean ± 1 SD) of 25OHD (nmol/l) and 24,25(OH)$_2$D (nmol/l) in 55 femoral neck fracture patients, 39 women and 16 men, and in age- and sex-matched healthy controls, 16 women and 6 men. Mann-Whitney's U-test. Conversion: SI units to traditional units: S-25OHD: 1 nmol/l ≃ 0.40 ng/ml, S-24,25(OH)$_2$D: 1 nmol/l ≃ 0.42 ng/ml

	Patients	Controls	*P*
Women			
S-25OHD	25.3±19.8	52.8±27.8	<0.001
S-24,25(OH)$_2$D	0.90±1.50	2.38±2.07	<0.01
Men			
S-25OHD	29.8±15.0	66.0±29.3	<0.02
S-24,25(OH)$_2$D	0.98±1.26	2.28±1.74	<0.02

Table 3. Histomorphometric values (mean ± 1 SD) in 36 female and in 14 male patients with a hip fracture compared with control values obtained from an age- and sex-matched group of 17 females and 13 males with no bone disease. Mann-Whitney's U-test, ns = not significant

	Patients	Controls	*P*
Females			
V_v (%)	12.2±3.8	13.9±5.6	ns
V_{vo} (%)	2.5±3.0	1.3±0.5	<0.05
OS (%)	22.5±11.7	16.7±7.2	<0.025
RS (%)	5.4±2.5	4.1±2.1	<0.02
Males			
V_v (%)	15.3±4.9	14.2±3.7	ns
V_{vo} (%)	5.5±8.0	1.4±0.9	<0.02
OS (%)	35.9±20.8	17.6±9.0	<0.02
RS (%)	5.9±2.4	3.6±1.7	<0.02

statistically significant difference in S-25OHD or in S-24,25(OH)$_2$D was observed between the patients with or without an increase in V_{vo}.

DISCUSSION

Osteomalacia is a bone disorder in which the mineralization of the organic bone matrix is disturbed. The mineralization process is controlled by vitamin D, and deficiency or impairment in the metabolism of vitamin D leads to accumulation of osteoid in the skeleton, i.e., osteomalacia (Chalmers 1968, Haussler & McCain 1977, Frame & Parfitt 1978, Habener & Mahaffey 1978). Many pathological conditions can lead to osteomalacia. Probably the most common causes of vitamin D deficiency and osteomalacia are intestinal malabsorption, inadequate diet and lack of exposure to sunlight (Chalmers et al. 1967, Chalmers 1968). Nilsson (1970) demonstrated that there was a high frequency of chronic alcoholism and previous gastrectomy among male hip fracture patients under 70 years of age.

In our series, there were 58 consecutive hip fracture patients who were operated on for their fracture. The patients were distributed over a time-span of 1 year which allowed for a possible seasonal variation in fractures.

The diagnosis of osteomalacia is usually based on clinical signs (bone pain and tenderness, muscular weakness and fractures), biochemical tests (decreased S-Ca and S-Pi, elevated S-ALP and decreased dU-Ca), roentgenology (decalcification of bones and Looser's zones) and histology (increased amount of osteoid and disturbed mineralization). The frequency of osteomalacia in femoral fractures varies from 0 to 37 per cent, partly depending on the criteria that are used in the diagnosis of osteomalacia (Aaron et al. 1974, Chalmers et al. 1969, Eid & Orth 1978, Gallagher et al. 1972, Hodkinson 1971, Jenkins et al. 1973, Wootton et al. 1979). Biochemical tests (S-Ca, S-Pi, S-ALP, dU-Ca) may be normal in osteomalacia (Anderson et al. 1966, Daw et al. 1979, Eid & Orth 1978, Jenkins et al. 1973), but histological examination indicating excessive osteoid confirms the diagnosis (Aaron et al. 1974, Anderson et al. 1966, Chalmers et al.

1967, Daw et al. 1979). Bone mineral content (Wootton et al. 1979) and bone mineral density (Alhava 1974) have been demonstrated to be diminished in femoral fracture patients. Studies in England have shown that the S-25OHD$_3$ level is decreased in hip fracture patients (Aaron et al. 1979, Brown et al. 1976, Daw et al. 1979), but Lund et al. (1975) could not find any difference in the serum levels of 25OHD$_3$ between Danish hip fracture patients and controls. The discrepancy between these results is explained by the fact that in Denmark food is rich in vitamin D (Lund et al. 1975). Serum alkaline phosphatase increases after fractures (Alhava 1974, Hosking 1978, Nilsson & Westlin 1972), but is unaffected by the presence of the fracture during the first week after the injury (Hosking 1978). A considerable decrease in serum calcium and an increase in serum phosphorus was demonstrated by Nilsson & Westlin (1972).

In the present study generally accepted laboratory tests for the diagnosis of osteomalacia were used. In addition to routine laboratory tests, the serum concentrations of 25OHD and 24,25(OH)$_2$D and histomorphometric values of the iliac crest cancellous bone were determined.

Biochemical findings indicating osteomalacia were frequent in our hip fracture patients. An increased S-ALP level with a decreased level of S-Ca or a decreased dU-Ca was recorded in 22 per cent of the female and in 13 per cent of the male patients. S-25OHD concentrations were significantly diminished in the hip fracture patients compared with age-matched normal controls. This is in agreement with Aaron et al. (1979), Baker et al. (1979) and Daw et al. (1979). Weisman et al. (1978) could not find any difference in S-25OHD or in S-24,25(OH)$_2$D between their fracture patients and elderly controls. Their elderly controls, although they were living in sunny climates, had very low serum vitamin D concentrations, which explains the discrepancy between their results and ours.

Histomorphometric analysis of undecalcified bone sections revealed an increase in the amount of osteoid in six out of 36 women (17 per cent) and in six out of 14 men (43 per cent). One woman and one man with normal S-Ca, S-Pi, S-ALP and dU-Ca had an increased amount of osteoid. Twenty per cent of our patients had biochemical findings (increased S-ALP with a decreased S-Ca and/or dU-Ca) and 24 per cent had histomorphometric values (V_{vo} over 3.4 per cent) indicating osteomalacia, but the correlation between these methods was not good. This is in agreement with Daw et al. (1979) and Jenkins et al. (1973). Thirteen out of 36 women and one out of 14 men had a V_v less than 10 per cent, indicating a considerable loss of bone. Two of these 13 women, but not the man, with a decreased amount of cancellous bone, had an increase in the amount of osteoid. Thus, 14 per cent of our osteoporotic hip fracture patients also had osteomalacia as indicated by histological criteria. Osteomalacia in osteoporotic patients has also been found by other authors (Aron et al. 1974, Chalmers 1968, Gallagher et al. 1972). Histological osteomalacia was relatively mild in our patients; only one woman and one man had a V_{vo} over 10 per cent (18 and 32 per cent, respectively). It has been suggested that a slightly increased amount of osteoid is of minor importance in the pathogenesis of femoral fractures (Chalmers et al. 1969). However, Faccini et al. (1976) found a significant relationship between fractures and the amount of osteoid. Many other studies support the important role of osteomalacia in the pathogenesis of femoral neck fractures (Aaron et al. 1974, Baker et al. 1979, Eid & Orth 1978, Gallagher et al. 1972, Jenkins et al. 1973, O'Driscoll 1973).

In our patients, there was only one with an evident reason for osteomalacia (a 29-year-old man with glutein enteropathy). There were two female patients in our series who had undergone partial gastric resection according to Billroth II 9 and 33 years earlier. Neither of them revealed evidence of osteomalacia in the histological study, although they had an increased level of S-ALP. A male alcoholic, 42 years old, had a slightly increased amount of osteoid (V_{vo} 6.1 per cent), but his biochemical parameters (S-Ca, S-Pi, S-ALP, dU-Ca) and the amount of trabecular bone (V_v 19.7 per cent) were normal. The most obvious cause of osteomalacia in our series was lack of vitamin D due to deficient diet and lack of exposure to sunlight. It is probable that the patients had a deficient diet, because hypoproteinaemia and anaemia were very frequent findings. It is probable also that the patients were deprived of exposure to sunlight due to the northern latitudes in which they lived. Especially institutionalized patients are at risk. Forty per cent of our patients were living in an institution when they suffered the fracture.

CONCLUSIONS

Osteoporosis was the main factor in the pathogenesis of hip fractures in our series. Immobilization, especially of institutionalized persons, was an important aggravating factor in the pathogenesis of osteoporosis and hip fractures in these patients. Osteomalacia was a common finding; it occurred in 24 per cent of the patients as indicated by histological criteria. Although osteomalacia was relatively mild in our patients it appears to play an important role in the pathogenesis of hip fractures in Finland. Osteomalacia combined with osteoporosis was also a common finding. An increased amount of osteoid was found in 14 per cent of the patients with a decreased amount of trabecular bone in the histomorphometric study. The most common cause of osteomalacia was probably deficiency of vitamin D due to inadequate diet and lack of exposure to sunlight.

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