PAPERS AND ORIGINALS

Vitamin D Deficiency, Spontaneous Fractures, and Osteopenia in Rheumatoid Arthritis

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Summary

Spontaneous, undisplaced fractures occurred in the long bones of five patients with longstanding rheumatoid arthritis. The results of biochemical, radiological, and dietary investigations in these patients were compared with those in a larger group of elderly women with rheumatoid arthritis without fractures. A significant association between skeletal rarefaction, calcium × phosphate product, and vitamin-D intake was shown in the whole group. Bone biopsies were performed in three patients with fractures, and histological evidence of osteomalacia was found in two patients. Dietary vitamin-D deficiency seems to play an important role in causing both the fractures and the osteopenia of longstanding rheumatoid arthritis.

Introduction

Spontaneous fractures occurring in the long bones are well recognized in patients with rheumatoid arthritis, whether or not they are receiving corticosteroid therapy (Baer, 1941; Haider, 1966; Taylor *et al.*, 1971). Generalized osteoporosis is considered to be an important factor in the pathogenesis of these fractures.

Nutritional osteomalacia has been reported in adults in this country (Gough *et al.*, 1964), and it may play an important part in skeletal rarefaction in the elderly (Exton-Smith *et al.*, 1966) and in the steep rise in femoral neck fractures with advancing age seen in the U.K. (Aaron *et al.*, 1974 a).

We report here five cases in which spontaneous fractures occurred in the long bones of patients with longstanding rheumatoid arthritis. A further group of elderly women with rheumatoid arthritis, in whom fractures had not occurred, was also studied. The results of biochemical, radiological, and dietary investigations performed on each group were compared.

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Patients and Methods

Five patients were studied who had sustained fractures, four involving the tibia and fibula and the fifth affecting the neck of the femur. Details of the patients are given in table I, and the fractures are illustrated in figs. 1-3. All the patients were postmenopausal women with longstanding rheumatoid arthritis and had been housebound for some years. One patient had received a small dose of corticosteroids for a year before admission. One fracture resulted from a minor fall, but in the other cases there was no history of trauma.

A further 12 female patients were selected who had not suffered fractures. All were over the age of 50 and had suffered from rheumatoid arthritis for more than 10 years. Three had been receiving corticosteroids equivalent to 10 mg of prednisolone for at least five years.

Bone biopsy specimens were taken from the iliac crest in three of the patients with fractures and were examined. Early morning fasting levels of serum calcium, phosphate, and alkaline phosphatase were determined on both groups of patients by AutoAnalyzer, the serum calcium by the cresolphthalein complexone method, serum phosphate by a modification of the technique described by Morgenstern *et al.* (1965), and alkaline phosphatase by a modification of the method of Robinson *et al.* (1971). The serum calcium was corrected using the formula of Parfitt (1974) and the calcium × phosphate product was then calculated. The 24-hour urinary excretion of calcium and hydroxyproline was measured in the patients with fractures, the hydroxyproline being estimated by the method described by Pennock *et al.* (1970). Bone mass was estimated from *x*-ray examinations of the femur and second metacarpal by the method of Barnett and Nordin (1960). The ratio of the combined thickness of the cortex to the width was calculated for both bones and the results added to give a peripheral bone score. A score of less than 88 was taken to indicate osteopenia (Barnett and Nordin, 1960).

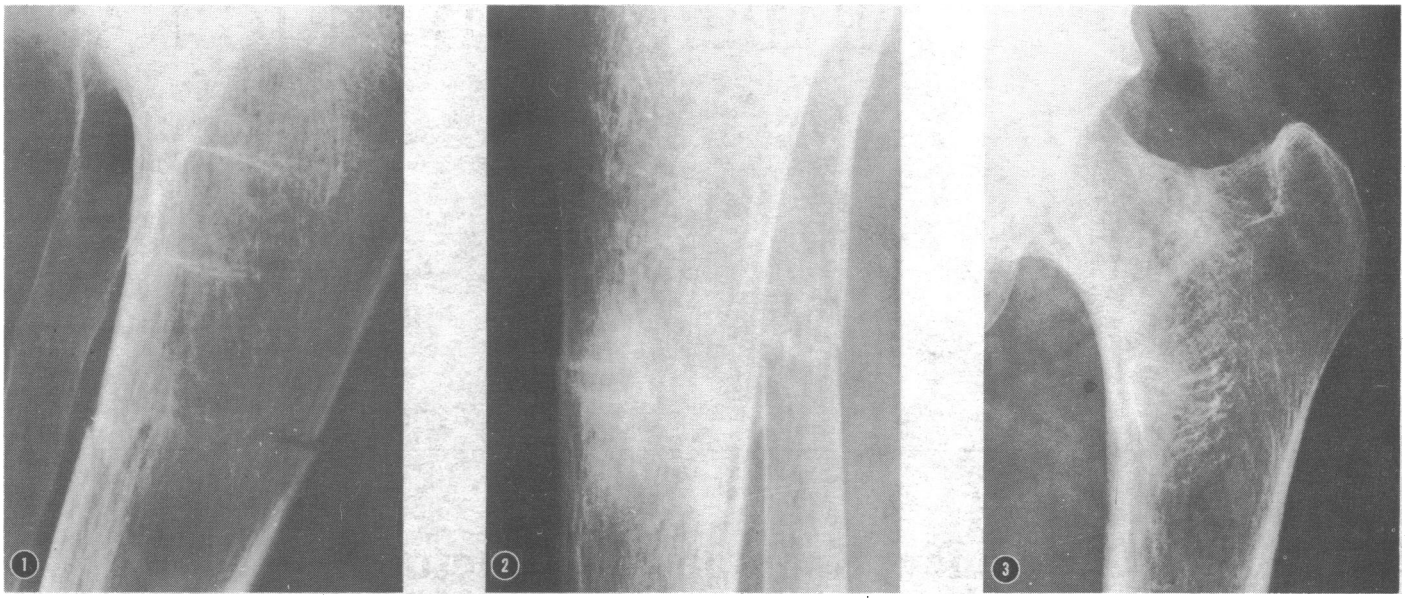

FIG. 1—Case 2. Recent undisplaced fracture of tibia occurring through a Looser's zone and showing thin cortical bone. FIG. 2—Case 1. Old undisplaced fractures of tibia and fibula with callus formation showing thin cortical bone. FIG. 3—Case 3. Undisplaced fracture of neck of femur with no callus formation at six weeks. Thin cortical bone is present.

TABLE I—*Details of Patients with Fractures*

Case No.	Age (yr)	Sex	Duration of Arthritis (yr)	Initial Symptoms and Signs	Radiographic Appearances on Admission	Corrected Serum Calcium (mg/100 ml)	Serum Phosphate (mg/100 ml)	Alkaline Phosphatase (K.A. Units)	24-hr Urine Calcium (mg)	24-hr Urine Hydroxyproline (mg/g creatinine)
1	70	F.	26	Minor fall, pain in right knee	Fracture right tibia, old fracture right fibula	8·1	3·0	21	31	77
2	60	F.	37	No trauma, pain in left knee	Fracture left tibia, old fractures right and left fibulae	8·8	2·7	16	165	60
3	54	F.	24	No trauma, pain in right hip	Basal fracture neck of left femur	9·2	3·0	25	121	62
4	70	F.	24	No trauma, pain in left knee	Fracture left tibia and fibula	8·9	3·1	12	60	60
5	75	F.	14	None	Old fracture left fibula	8·0	2·8	30	50	—

A dietary history was obtained from each patient with particular reference to the average daily intake of vitamin D, calcium, protein, and calories.

Results

Two of the three bone biopsy specimens showed osteomalacia (cases 1 and 3), which in case 3 was associated with changes of mild hyperparathyroidism. In case 2 the bone trabeculae were thin, but the amount of osteoid was normal. A quantitative assessment of calcified bone and osteoid was made on each specimen, the normal values (mean ± S.D.) being taken as 13·39 ± 8·58% for calcified bone in patients of this age group and sex and less than 0·6% for osteoid. In the biopsy specimen from case 1 there was 11·94% calcified bone and 3·4% osteoid, in that from case 3 there was 17·54% calcified bone and 1·75% osteoid, and in that from case 2 there was 11·22% calcified bone and 0·34% osteoid.

The calcium × phosphate product in the group of patients with fractures ranged from 22·4 to 27·6 (mean 25·1). The serum alkaline phosphatase was raised in four cases, and in three it was greater than 20 K.A. units. These included the two patients with evidence of osteomalacia in the bone biopsy specimen. The 24-hour urinary excretion of calcium was low in all the patients (31-165 mg), and the excretion of hydroxyproline was increased (60-77 mg/g creatinine). In the non-fracture group the calcium × phosphate product ranged from 24·5 to 45 (mean 35·6) and only two values were less than 29. The serum alkaline phosphatase was within normal limits.

Blood urea and faecal fats were measured, and no evidence of renal impairment or malabsorption was found in any of the patients of either group.

None of the diets were deficient in calcium, protein, or calories. In the group of patients with fractures the mean vitamin-D intake was 35·5 IU (range 19·7-40·1 IU) and in those without fractures 85·5 IU (range 28·7-173 IU). The difference was due to a reduced consumption of all vitamin-D-containing foods, particularly of margarine and eggs, in the group with fractures. The results of this survey were compared with the Department of Health and Social Security recommendations for women of this age group (Department of Health and Social Security, 1969). They suggest an average daily intake of 100 IU of vitamin D, 500 mg of calcium, 50 g of protein, and 2,000 calories. When all the patients were taken together the vitamin D intake showed a statistically significant correlation with the calcium × phosphate product ($r = 0·804$; $P < 0·001$) (fig. 4).

Four patients with fractures had radiological evidence of osteopenia (peripheral bone score of less than 88), and in three cases this was marked. In cases 1 and 2 there was also radiological evidence of osteomalacia in that the fractures appeared to occur through a Looser's zone (see figs. 1 and 2). Seven patients in the

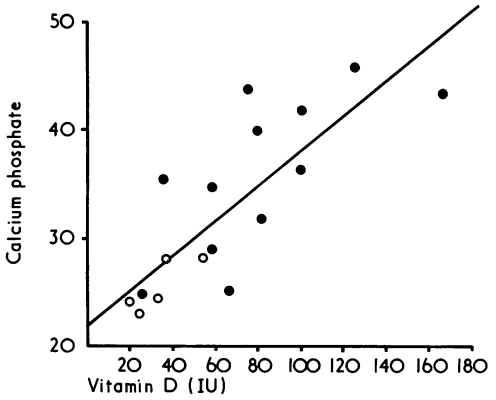

FIG. 4—Relationship between calcium × phosphate product and vitamin-D intake. Highly significant correlation is shown (r = 0·804; P<0·001). ○ = Patients with fractures. ● = Patients without fractures.

TABLE II—*Comparison of Calcium × Phosphate Product and Vitamin D Intake in Patients with and without Osteopenia*

Peripheral Bone Score	No. of Patients	Mean Age (yr)	Mean (Range) Calcium × Phosphate Product	Mean (Range) Daily Vitamin D Intake (IU)
<88	11	66	29·6 (22·4-43)	57·5 (19·7-107·6)
>88	6	64	39·1 (27·6-45·0)	94·7 (37·1-173·1)

Correlation between osteopenia and vitamin-D intake: r = 0·58; 0·05>P>0·10.

non-fracture group also had osteopenia. When the patients were taken together there was a significant correlation between the presence of osteopenia and the calcium × phosphate product (r = 0·58; 0·05>P>0·10) (table II).

Discussion

Spontaneous fractures are known to occur in rheumatoid arthritis, and generalized osteoporosis had been considered to be the main factor in their pathogenesis (Haider *et al.*, 1966). Generalized osteopenia (skeletal rarefaction as measured from an *x*-ray film; Nordin, 1973) can complicate rheumatoid arthritis per se (McConkey *et al.*, 1962), but it may be aggravated by corticosteroid therapy (Boland *et al.*, 1950) and by the age and sex of the patient (Saville *et al.*, 1967).

We have described five cases of spontaneous, undisplaced fractures occurring in patients with longstanding rheumatoid arthritis. Two patients showed histological evidence of osteomalacia on bone biopsy, and the remainder had biochemical findings suggestive of osteomalacia. The survey of a larger group of elderly women with rheumatoid arthritis has extended these findings and shows a significant association between osteopenia, low calcium × phosphate product, and low vitamin-D intake. This suggests that dietary vitamin-D deficiency was an important cause of the fractures and skeletal rarefaction in our patients.

Exton-Smith *et al.* (1966) have suggested that dietary deficiency of vitamin D causing osteomalacia plays an important part in skeletal rarefaction in the elderly, and this seems to be partly responsible for the steep rise in femoral neck fractures with advancing age seen in the U.K. (Aaron *et al.*, 1974 a). The osteomalacia found in patients with femoral neck fractures has shown a seasonal variation, and this has been attributed to the variation in the hours of sunlight (Aaron *et al.*, 1974 b). It is probable that vitamin-D deficiency insufficient to produce definite osteomalacia can cause osteopenia (Nordin *et al.*, 1972).

All the patients with fractures in this study had been housebound for a long time, which is common in many people disabled by rheumatoid arthritis. The dietary deficiency of vitamin D shown up by the survey is therefore all the more important. Major food sources of vitamin D are margarine, sardines, eggs, and milk products, but as the low vitamin-D intake was found to be partly due to economic reasons we suggest that a practical way of preventing vitamin-D deficiency in these disabled patients is to prescribe a preparation such as vitamin capsules (*B.P.C.*), which contain 300 IU of vitamin D.

Osteopenia occurs early in active rheumatoid arthritis. Rarefaction of the bones in the neighbourhood of an affected joint is considered to be one of the first radiological signs of rheumatoid arthritis (Soila, 1958) and there is diffuse demineralization affecting the whole skeleton early in the disease (Duncan *et al.*, 1965). The cause of this is not known though a lymphokine factor producing bone resorption may be one of the factors involved (Horton *et al.*, 1972). In longstanding rheumatoid arthritis, however, our results show that when the patients are elderly and become housebound dietary vitamin-D deficiency assumes an important role in the production of osteopenia and spontaneous fractures

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