Osteomalacia in rheumatoid arthritis

SUSAN O'DRISCOLL AND MICHAEL O'DRISCOLL

From the Orthopaedic Department, Bristol Royal Infirmary

SUMMARY Fifty-four patients with rheumatoid arthritis and severe osteomalacia were found to have considerable bone and general deficiency problems. In 46 of them 14 stress fractures occurred and 32 minimal trauma fractures necessitating admission to hospital. Radiological abnormalities of absorption were found in nearly 25% of the total, implying that dietary factors alone are not always responsible for osteomalacia in patients with rheumatoid arthritis. A high index of suspicion is necessary in the diagnosis of osteomalacia in patients with rheumatoid arthritis, so they may benefit from treatment.

Spontaneous and stress fractures have been reported in patients with rheumatoid arthritis (RA), whether or not they were receiving steroids (Haider and Storey, 1962; Taylor *et al.*, 1971). Generalised osteoporosis has been considered important in their aetiology. Osteomalacia in RA has been reported infrequently, but Maddison and Bacon (1974) reported 5 cases of RA with osteomalacia presenting with spontaneous fractures. They drew attention to its occurrence and how easily it may be overlooked. In their series dietary deficiency was thought to be the major cause of the osteomalacia.

The elderly British population has been shown to be in a chronic state of hypovitaminosis D (Exton-Smith *et al.*, 1966; Chalmers *et al.*, 1967; Stanbury *et al.*, 1970). This is due to dietary inadequacies of vitamin D and the geographical position of Great Britain in relation to the ultraviolet in sunlight.

Osteomalacia occurs in malabsorption states (Salveson and Boe, 1973), renal disease (Fourman and Royer, 1968); liver disease (Sherlock *et al.*, 1966), and during anticonvulsant therapy with phenytoin (Kruse, 1968). The symptoms of osteomalacia are well known, consisting of weakness, lassitude, and bone pain in severe cases. These symptoms of osteomalacia may be overlooked in the plethora of other symptoms in RA.

Recent work on proximal femoral fractures (Chalmers, 1970; O'Driscoll, 1973; Jenkins *et al.*, 1974) has shown how common osteomalacia is among elderly people with fractures. Orthopaedic departments see most of the cases that present as pathological fractures.

The present study is based on 54 patients with RA and osteomalacia leading to pathological fracture or severe bone pain seen in the Orthopaedic Department at Bristol Royal Infirmary over a period of 2½ years.

Patients and methods

Fifty-four patients with RA and severe osteomalacia without any renal or liver disease who presented to the Orthopaedic Department at Bristol Royal Infirmary with pathological fractures or severe bone pain over a period of 2½ years were studied. There were 48 females and 6 males, the average age was 62 ± 7 years. They had all had RA for a minimum of 10 years. None of the 54 patients were receiving anticonvulsant therapy.

All 54 patients had received steroids at some stage of their disease. Twenty-one were on steroids at the time of presentation. All the patients had received most of the common anti-inflammatory drugs at some stage of their disease. Nine patients had had chrysotherapy, but none had been given penicillamine or cytotoxic agents. The majority of the 54 patients presented with pathological and stress fractures, the rest with generalised bone pain (Table 1).

Table 1 *Presentation of patients*

<i>Symptoms</i>	<i>Number</i>
Pelvic fracture	16
Proximal femoral fracture	8
Tibial fractures	8
Stress fracture	14
Generalised bone pain	8
Total	54

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Correspondence to Mr M. O'Driscoll, FRCS, Leighton Hospital, Leighton, Crewe CW1 4OJ.

2 O'Driscoll, O'Driscoll

Seven of the 54 patients, 3 male and 4 female, had undergone partial gastrectomy in the past. These 7 all presented with proximal fractures of the femur.

INVESTIGATIONS

Haematological and chemical pathological investigations were performed on all 54 patients. All the patients had haemoglobin estimation and a full blood count performed. Serum calcium, with correction for protein (Dent, 1962), phosphorus and alkaline phosphatase and protein levels were measured. Urea and electrolytes were determined, and all patients had a 24-hour creatinine clearance test performed. Serum iron and total iron binding capacities (TIBC), serum B₁₂, and red cell folate levels were measured. Liver function tests including 5 nucleotidase levels were performed, as was a 5-hour xylose excretion test.

If the 5-hour xylose excretion test was abnormal, 3-day faecal fat studies were performed, and a small bowel follow-through barium meal was obtained, except in the 7 patients who had had previous partial gastrectomy. If the B₁₂ level was low a Schilling test was carried out. All patients had 24-hour collections of urine for calcium excretion for 2 days and a modified Whittle vitamin D saturation test (Whittle *et al.*, 1969) modified by O'Driscoll (1973).

Skeletal surveys were carried out on all the patients. In the absence of Looser zones, which were taken as diagnostic of osteomalacia, bone biopsy from the iliac crest was performed either on its own or during operation.

Results

RADIOLOGY

All 54 patients had severe loss of bone density and were diagnosed as being osteoporotic; 39 had Looser zones, 31 being multiple.

Looser zones (Fig. 1) are diagnostic of osteomalacia (Milkman, 1930; Fourman and Roger, 1968; Chalmers, 1970), the differential diagnosis of these pseudofractures being the infractions of Paget's disease and stress fractures occurring in fragilitas ossium. Paget's disease was not present in any of these patients and none had the rare disease of fragilitas ossium.

Table 2 Sites and numbers of Looser zones

Site of Looser zone	Number of patients
Pelvis	4
Ribs	4
Multiple sites	31
Total	39

Fig. 1 Looser zone in the forearm of a patient with rheumatoid arthritis: note destruction of wrist

Multiple Looser zones were present in 31 of the 54 patients (Table 2). So-called steroid or osteoporotic stress fractures were seen in 16 patients; all of these 16 had Looser zones elsewhere. Fig. 2 shows a stress fracture in a fibula with a Looser zone in the contralateral femur (Fig. 3), and some 5 days later a spontaneous fracture is shown. Fig. 4.

Fig. 2 Apparent stress fracture in a patient with rheumatoid arthritis

Fig. 3 Looser zone of femur before fracture

Fig. 4 Same patient after Looser zone had given way to become a complete fracture

HAEMATOLOGY

The results of the patients' haemoglobin film, serum iron, total iron binding capacity, serum B_{12} , and red cell folate are shown in Table 3. Only 14 patients had low serum B_{12} . All of these had an abnormal Schilling test. All 7 patients who had undergone partial gastrectomy fell in this group.

CHEMICAL PATHOLOGY

Urea and electrolytes were normal in all the patients, as were their bilirubins, transaminases, and 5-nucleotidase. The abnormal results obtained for calcium, phosphate, calcium/phosphate product, alkaline phosphatase, total protein, and 24-hour urinary calcium excretion are shown in Table 4.

Table 3 Haematological results

Test	Mean	Standard deviation	Normal
Haemoglobin Film	11.9 g/dl Normal 48 patients, microcytic 5 patients, megaloblastic 1 patient	0.5	
Serum iron	29.4 µg/100 ml	9.8	120-250
TIBC	234 µg/100 ml	12	200-350
B_{12}	125 µg/100 ml	37	Above 166 µg
Red cell folate	134 µg/100 ml	31	Above 166 µg

Conversion to SI: Serum iron and TIBC 1 µg=0.179 µmol/l.

Table 4 Chemical pathology

Test	Average for 54 patients	Standard deviation	Normal
Calcium	8.17 mg/100 ml	0.21	8.8—10.7
Phosphate	2.41 mg/100 ml	0.19	2.8—4.5
Calcium/phosphate product	21.4	3.1	
Alkaline phosphatase	18.2 King-Armstrong units/100 ml	8.4	Below 12
Total protein	7.1 g/100 ml	0.24	7.0—8.0
24-hour urinary calcium excretion (average of 2)	63.4 mg/24 h	18.8	200—350

Conversion to SI: Calcium 1 mg/100 ml=0.25 mmol/l. Phosphate 1 mg/100 ml=0.323 mmol/l. Total protein 1 g/100 ml=10 g/l. 24-hour urinary calcium 1 mg/24 h=0.025 mmol/24 h.

Thirty-four of the 54 patients had xylose excretion below 25% (normal >25% excretion). Of these 34 patients with abnormal xylose excretion 7 had had partial gastrectomy, leaving 27 patients without previous gastrointestinal surgery with RA and abnormal xylose excretion tests. None of these patients had abnormal results for their 3-day faecal fats.

MODIFIED WHITTLE TESTS

All 54 patients had a modified Whittle test performed (Whittle *et al.*, 1969) modified by O'Driscoll (1973). The Whittle test consists of an intravenous load of vitamin D₃ and estimation of the serum phosphate before the injection and again at 4 days. If the serum phosphate rises by more than 25%, vitamin D deficiency is indicated. The modification used is an oral daily load of 50 000 units of vitamin D for 7 days with measurement of the serum phosphate at the beginning and end of the test. A rise in serum phosphate of 25% or over is indicative of vitamin D deficiency.

All 54 patients in the present study responded by a rise of 50% or more in serum phosphate after 7 days.

BONE BIOPSY SPECIMENS

Fifteen bone biopsy specimens were examined by von Kossa staining of undecalcified sections, 3 or more osteoid lamellae being suggestive of osteomalacia (Woods, 1966). The largest number of lamellae was 4, the maximum 7 (Table 5).

Table 5 Osteoid lamellae

Number	3	4	5	6	7
1		5	6	2	1

Fig. 5 Small bowel meal of patient with osteomalacia. Looser zone in pelvis; shows flocculation, segmentation, and dilatation of small bowel. Radiological malabsorption pattern

ABSORPTION STUDIES

The 27 patients with RA who had abnormal xylose excretion without previous partial gastrectomy underwent barium studies with a small bowel follow-through examination. Fourteen of these were normal. Thirteen patients showed radiological evidence of malabsorption with flocculation, dilatation, and segmental thickening of the mucosal fold (Fig. 5).

DIET

An assessment of dietary vitamin D content was attempted by means of the tables and values in Samson-Wright (1961). In none of these patients was the dietary intake of vitamin D greater than 90 IU a day, average intake 44 ± 15 . However, of 50 other patients without RA presenting for hip and knee surgery in the same period none had an intake of adequate vitamin D. Their average was 49 ± 17 . These patients all had dietary vitamin D deficiency but none had osteomalacia.

ULTRAVIOLET EXPOSURE

This could not be measured. Just over half (28) patients were totally house bound, and the remainder were only less so.

Discussion

All 54 patients had RA with evidence of osteomalacia. Thirty-two patients developed fractures precipitating their presentation. Fracture of major bones is a catastrophe to the patient with RA, the sequelae of which led to the death of 4 patients out of the 54 studied and permanent loss of ambulatory function in 5 patients.

Osteomalacia was associated with stress fractures in 14 patients and bone pain in 8 patients. Osteomalacia must always be considered as a possible cause of stress fractures and must be excluded. Maddison and Bacon (1974) have drawn attention to this and the present study reinforces the fact that osteomalacia may be one of the underlying factors in stress and spontaneous fractures in patients with RA.

Dietary deficiency of vitamin D certainly played a major part in the causation of the osteomalacia, but absorption abnormalities were found in a proportion of cases. Absorption abnormalities of the small bowel have been found in RA (Toivonen *et al.*, 1964; Siurala *et al.*, 1965; Patterssen *et al.*, 1970). Malnutrition itself may cause malabsorption (Herskovic, 1969), as may the drugs used for the treatment of RA, which may also cause malabsorption (Falcon and Saunders, 1968; Kendall *et al.*, 1971).

A high incidence of haematological abnormalities were found in these patients in spite of normal blood counts, and this emphasises their deficiency problems. Certainly the 54 patients studied had dietary deficiencies in addition to the other effects of their rheumatoid arthritis. Gastric upsets due to anti-inflammatory agents, difficulty in feeding and preparing food, and their relatively poorer economic situation all tended to increasing deficiency problems. Dietary supplementation of vitamin D would seem to be mandatory in this group of patients. They also had little exposure to ultraviolet light because of their lack of ambulation and being house bound.

In the present series deficiencies of diet have been found to be associated with abnormalities of absorption. This amounted to nearly 25% (13 out of 54) who had absorption abnormalities as shown by the barium studies. One of these patients had a large bowel malignancy from which she eventually died. Osteomalacia in patients with RA may be commoner than is recognised and can easily be mistaken for osteoporosis. Looser zones appear late in osteomalacia and nonspecific loss of bone density may be the only early feature. This being common to both osteoporosis and osteomalacia.

Certainly all patients with RA who develop

spontaneous stress fractures should be extensively investigated for osteomalacia, including a bone biopsy if necessary, before a diagnosis of osteoporosis is acceptable. Osteomalacia is easily treated and may by its treatment stop further development of spontaneous or stress fractures. Further, it must not be assumed that dietary deficiency is the only cause of osteomalacia in a patient, since a careful search may reveal other disease. No conclusions as to the incidence of osteomalacia in RA may be drawn from this series except that it can occur, and dietary causes may not be the only factors.

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