

## CONCISE REPORT

# Stress fractures in rheumatoid arthritis: a case series and case-control study

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**Objective:** To review cases of stress fracture in patients with rheumatoid arthritis (RA) presenting to our service over a 10 year period; to identify possible risk factors and test these in a case-control study.

**Methods:** A retrospective case note review of all patients with a final diagnosis of stress fracture, presenting between 1990 and 1999 was performed. A case-control study of consecutive patients with RA, matched for age, sex and duration of disease, attending the same clinics.

**Results:** Case series: 24 stress fractures were identified in 18 patients, representing 0.8% of the RA clinic population; all were women, median age 69.5 years (range 47–79). Bone mineral densitometry showed median T scores of  $-3.06$  and  $-2.27$  SD at the hip and lumbar spine, respectively. Case-control study: In the stress fractures group, past steroid doses were higher ( $p=0.003$ ). No significant differences in the bone mineral density (BMD) T score at the hip or lumbar spine were found ( $p=0.59$ ,  $p=0.77$ ).

**Conclusions:** Stress fractures are a significant cause of morbidity in RA. Diagnosis is often delayed and presentation can be misleading. Past steroid use, particularly at higher doses, confers an increased risk of stress fracture, but the increased risk is not attributable to osteoporosis as assessed by BMD.

Stress fractures occur when a repetitive load overcomes the reparative ability of bone. This may occur when strenuous repeated force is applied to normal bone or when normal force is applied to bone that is deficient in mineralisation or in elastic resistance. A number of authors have emphasised the difficulty of diagnosing long bone stress fractures in rheumatoid arthritis (RA)<sup>1,2</sup> and, others, the difficulty with pelvic fractures.<sup>3–5</sup> In particular, stress fractures are frequently misdiagnosed as an exacerbation of inflammatory disease.<sup>2</sup> The delay in diagnosis may lead to significant morbidity.

Although stress fractures were described in RA before the introduction of corticosteroid treatment,<sup>6</sup> the association with the use of corticosteroids was reported within a few years of their introduction.<sup>7</sup> Hooyman *et al* reported corticosteroid use as risk factor for osteoporotic fracture in their population based study of RA, together with disability and thinness.<sup>8</sup> Methotrexate has also been proposed as a risk factor for stress fracture in patients with inflammatory arthritis.<sup>9</sup> There is some conflicting evidence from animal studies about the effects of low dose methotrexate on bone metabolism,<sup>10</sup> and evidence that high dose methotrexate in childhood oncology treatment is associated with a methotrexate osteopathy.<sup>11</sup> However, this has not been studied in RA in a controlled fashion.

In this report we review stress fractures in patients with RA presenting to our service over the period 1990–99. We describe their presentation, identify any possible risk factors for stress fracture, and then test the possible risk factors in a case-control study. The case-control study used consecutive age and sex matched controls with RA attending the same clinics.

## METHODS

The rheumatology department maintains two databases, Letts and Coddie, which contain records of all outpatients and inpatients, respectively. These were searched for all references to stress fracture or insufficiency fracture from the period 1990 to 1999. Control subjects with RA were collected consecutively from general rheumatology clinics by one consultant (PNP) and were matched for age within 2 years, sex, and disease duration. Case notes were reviewed using a structured proforma to collect information on demographic details and features of their RA, including disease duration, seropositivity for IgM rheumatoid factor, radiographic erosions, and previous lower limb arthroplasty. Information about the presentation, site, and effects of the fracture was recorded. Further information collected included results of bone densitometry measurement, age at menopause, weight, height, and levels of disability as measured by the Steinbrocker index. Data were entered into a database using EPI INFO version 6. Comparisons were made using the Kruskal-Wallis test and the Fischer exact test. Local research ethics committee approval was obtained.

## RESULTS

### Subjects

Eighteen patients with stress fracture were identified from a review of rheumatology departmental databases. Eighteen control subjects with RA, matched for age, sex, and disease duration, were gathered from consecutive general rheumatology clinics by one consultant (PNP). All subjects were female.

### Case series subjects

All 18 cases identified were women, with a median age of 69.5 years (range 47–79) and a median duration of RA of 20 years (range 8–50). Table 1 shows characteristics of the patients, their disease, and steroid treatment. Six subjects (33%) died within 8 years of fracture.

### Fractures

The 18 fractures were all in the lower limb or pelvis: tibia alone (6); fibula alone (3); tibia and fibula (2); femur (2); pubic ramus (5). All patients reported symptoms, which were of acute onset in 7 and gradual onset in the remaining 11. Symptoms most commonly reported were local pain (18),

**Abbreviations:** BMD, bone mineral density; BMI, body mass index; RA, rheumatoid arthritis

**Table 1** Characteristics of patients with stress fracture and control subjects with RA

Factor	Subjects	Controls	Significance (p value)
Age (years), median (range)	69.5 (47–79)	68 (49–79)	0.41
Disease duration (years), median (range)	20 (8–50)	19.5 (3–31)	0.37
Rheumatoid factor positive	13	17	0.18
Steinbrocker index			
I	0	2	0.14
II	4	7	
III	14	9	
IV	0	0	
Arthroplasty	7	6	0.73
Age at menopause (years), median (range)	47 (42–56)	47 (34–52)	0.60
Smokers	5	6	0.81
Body mass index, median (range)	23.3 (17.5–33.2)	22.4 (12.8–34)	0.41
<i>Use of steroid treatment</i>			
Current oral steroid treatment	11	8	0.32
Ever used oral steroid treatment	14	7	<b>0.02</b>
Maximum dose (mg/day), mean (SD)	10.4 (8.16)	4.0 (4.5)	<b>0.02</b>
Average dose (mg/day), mean (SD)	6.0 (3.2)	2.6 (2.9)	<b>0.003</b>
Duration of oral steroid treatment (months), mean (SD)	57 (75)	22.4 (40)	0.06
Intravenous steroid treatment	1	0	0.8
Intramuscular steroid doses	4 (3.9)	5.6 (3.8)	0.3
Intra-articular steroid doses	4.3 (5.4)	0.13 (0.5)	<b>0.0001</b>
<i>Bone mineral density</i>			
Femoral neck mean T score	−3.06	−2.91	0.59
Femoral neck mean Z score	−1.55	−1.04	0.10
Lumbar spine mean T score	−2.27	−2.28	0.77
Lumbar spine mean Z score	−1.30	−0.87	0.18

difficulty weight bearing (15), swelling (10), and erythema (5). The initial radiograph was reported as normal in one case and the diagnosis of stress fracture was made by isotope bone scan. The delay to diagnosis from first symptoms was a median of 4 (range 1–12) weeks. Recovery to the level of activity before symptoms began had a median duration of 4 (range 2–12) weeks. Four patients were managed with plaster casting, and rest only indicated for the remainder.

#### Risk factors for osteoporosis and fracture

Subjects were not consistently of low body mass index (BMI) (table 1). Median age at menopause was 47 years (range 42–56), and 5/18 subjects were smokers. Eleven of the 18 subjects were current users of oral corticosteroid treatment, and 14 had used such treatment at some time in the past. Table 1 gives details of previous oral steroid treatment. Only one subject had ever received intravenous steroid treatment, whereas seven subjects had received a median of three doses of intramuscular steroid of any type (range 0–10) and 2 (0–20) intra-articular steroid injections. Twelve of the subjects had undergone dual x ray absorptiometry scanning. Median bone density at the hip showed a T score and Z score of −2.80 and −1.56, respectively, with figures of −2.44 and −1.15 at the lumbar spine. Sixty per cent had a T score of −2.5 or lower at the hip and 50% at the spine.

#### Control subjects

Control patients were matched for age ( $p = 0.41$ ), sex (all female), and disease duration ( $p = 0.37$ ) (table 1). A similar frequency of seropositivity for rheumatoid factor at a titre of 1 in 80 or higher was found ( $p = 0.18$ ). No differences were found in the level of disability according to the Steinbrocker index ( $p = 0.14$ ) or in rates of previous arthroplasty ( $p = 0.73$ ) compared with subjects with stress fracture.

#### Comparison of risk factors for osteoporosis and fracture

A comparison of risk factors for osteoporosis and fracture showed no significant difference in age at menopause

( $p = 0.60$ ), frequency of smoking ( $p = 0.81$ ), or BMI ( $p = 0.41$ ) (table 1). Steroid usage was significantly more frequent in the subjects than controls (14/18 v 7/18,  $p = 0.02$ ). Maximum and average doses of oral corticosteroids were significantly higher in the subjects than in the controls ( $p = 0.02$ ,  $p = 0.003$ ). Bone mineral density (BMD), however, did not differ significantly between cases and controls, either at the hip or the lumbar spine ( $p = 0.59$ ,  $p = 0.77$ , respectively). There were no differences in rates of current (8/18 v 8/18  $p = 0.74$ ) or previous (12/18 v 15/18  $p = 0.44$ ) methotrexate treatment or median methotrexate dose ( $p = 0.55$ ).

#### DISCUSSION

As far as we know, this is the first case-control study to examine the features of, and risk factors for, insufficiency fractures in patients with RA. We have demonstrated that past history of steroid use, particularly at higher doses, is an identifiable risk factor for stress fracture in such patients, regardless of the patient's BMD.

We have shown that these fractures are not uncommon, and are a significant cause of morbidity in patients with RA. We identified 24 stress fractures in 18 patients over a decade, 0.8% of the population under study. The retrospective nature of this study and the acknowledged difficulty in making such a diagnosis<sup>1–12</sup> mean that this figure almost certainly underestimates the true prevalence. Plain radiographs taken in the early period after fracture often do not demonstrate the fracture,<sup>13</sup> whereas isotope bone scans and magnetic resonance imaging may be more sensitive,<sup>14,15</sup> although these are not universally in routine use.

The anatomical sites of the stress fractures in our series, their clinical presentations, and effect upon the patients are similar to those in other studies.<sup>16,17</sup> Multiple fractures have been shown previously to be relatively common.<sup>17</sup> The burden of morbidity borne by patients with such fractures has been previously described, but the apparently high mortality rate shown in this study is new. As the cases were collected retrospectively we were unable to determine whether this is higher than in control patients.

### Key messages

- Stress fractures in RA are not rare but are difficult to diagnose.
- Development of stress fractures is associated with past steroid use.
- Low BMD alone does not explain the occurrence of stress fractures.

The development of stress fractures may represent either fatigue fracturing or insufficiency fracturing. Fatigue fractures occur when abnormal stress is placed on normal bone, whereas insufficiency fractures occur when abnormal stresses act on bone with deficient elastic resistance. In the case of stress fractures in RA it is normally considered that these are insufficiency fractures. We have shown that conventional risk factors for low trauma fracture do not explain the occurrence of insufficiency fractures in patients with RA.

Previous studies<sup>16–18</sup> have suggested that osteoporosis, or low BMD, may explain the risk of stress fracture in RA. Our study, however, suggests that this is not the case. Bone density measurement was low in both groups, but no lower in those with fracture than in those without. Corticosteroids may exert their effect through other influences on bone architecture or modelling, as the increased risk of fracture does not appear to be mediated through effects associated with changes in BMD alone.

Previous, uncontrolled studies have suggested that factors such as previous surgery<sup>16</sup> may predispose to stress fracture in patients with RA. Our results suggest that these are no more common in patients sustaining such fractures than in controls, and may merely reflect coincidental features of longstanding RA. We failed to confirm the previous hypothesis based on animal work and case reports that methotrexate treatment is a risk factor for stress fracture.<sup>9–11</sup> Owing to our study design, we were unable to explore the effect of disease duration on risk of fracture.<sup>16</sup>

Clinicians should maintain a high degree of awareness of the possible presence of stress fracture in patients presenting with an increase in pain at a single site, particularly when the pain is periarticular in origin. Initial plain films may not be adequate to diagnose such fractures; further imaging may be necessary. The mechanism of action of steroid on bone in

patients with RA that confers the excess risk of stress fracture requires further study.

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