Rheumatoid arthritis, corticosteroid therapy and hip fracture*

C Cooper, C Coupland, M Mitchell

Abstract

Objective—To identify the risk of hip fracture in patients with rheumatoid arthritis and those taking corticosteroids.

Methods—In a population based case-control study, we compared 300 consecutive patients with hip fracture aged 50 years and over from a defined district and 600 age and sex matched community controls.

Results—The risk of hip fracture was increased in patients with rheumatoid arthritis (odds ratio (OR) 2·1; 95% confidence interval (CI) 1·0 to 4·7) and those receiving corticosteroids (OR 2·7; 95% CI 1·2 to 5·8). The risk attributable to rheumatoid arthritis was markedly reduced by adjusting for functional impairment, while that for steroid use remained after adjusting for body mass index, smoking, alcohol, and functional status.

Conclusions—Hip fracture risk is approximately doubled amongst patients with rheumatoid arthritis and among those taking steroids. These risk increases are, to some extent, independent of each other. In rheumatoid arthritis, the risk was most closely associated with functional impairment, whereas steroid use did not appear to be confounded by this variable.

The occurrence, skeletal distribution, clinical importance and cause of generalised osteoporosis in rheumatoid arthritis remains controversial.[1-12] Several reports have suggested a tendency to bone loss throughout the skeleton in patients with the disorder,[2 3 6] but the sites at which loss is most pronounced remain uncertain. Other studies report that patients with rheumatoid arthritis have no reduction in axial bone density unless they are treated with corticosteroids.[11 12] The major clinical consequence of any generalised reduction in bone density among such patients would be fracture, and hip fracture is the most dramatic of the fractures associated with osteoporosis. There are, however, few data on hip fracture risk among patients with rheumatoid arthritis.[13 14] Furthermore, the relative contributions to the development of fractures made by corticosteroid therapy, functional impairment, or the rheumatoid disease process itself are unclear. In the only previous controlled study of the incidence of hip fracture in patients with rheumatoid arthritis[13] the relative risk for hip fracture was significantly, but modestly, increased. If this increase in hip fracture risk could be confirmed, and its causes delineated, more effective strategies could be designed to retard age related bone loss in patients with rheumatoid arthritis. We have therefore examined the influence of rheumatoid arthritis on the risk of hip fracture in a population based case-control study.

Patients and methods

The case group comprised 300 patients (60 men and 240 women) aged 50 years and over who were admitted sequentially to an orthopaedic unit over an 18 month period with fracture of the proximal femur,[15] and who were able to pass an abbreviated mental test.[16] Patients in the study group were compared with 600 community controls, resident in the same district, who were selected from the register of Hampshire Family Practitioner Committee. Controls were matched to cases by sex and age within four years. The rate of response among controls was 71% of those contacted. When a control refused to participate or failed the mental test score a substitute was selected.

Each case-control set was visited by one of three trained interviewers. Cases were interviewed in hospital within 10 days of admission. Controls were interviewed at home within three months of their matched case (68%) or during the corresponding quarter one year later (32%).

At interview, information included a previous medical history. The patients who reported that they had previously been diagnosed by a physician as suffering from rheumatoid arthritis had their hospital or general practice records screened for documentation of the American Rheumatism Association (ARA) criteria.[17] Patients were defined as suffering from rheumatoid arthritis if they met the criteria for definite or classical disease or if deformity typical of the disorder was apparent. Hospital records were only available for the cases, and five were identified who reported rheumatoid arthritis, but in whom the diagnosis was not verified by record review. Although these individuals were classified as non-exposed for most of the analyses, the relationship between rheumatoid arthritis and hip fracture was also examined when these five subjects were included. Specific enquiry was also made as to current

MRC Environmental Epidemiology Unit, Southampton General Hospital, Southampton SO9 4XY, United Kingdom
C Cooper
C Coupland
M Mitchell
Correspondence to: Dr Cooper.

use of oral corticosteroids. Other potential risk factors recorded at interview included body weight and height, cigarette smoking and alcohol consumption. Dependence in daily living activities was assessed using the six point Katz index of activities of daily living.[18] This ascertains the degree of independence in feeding, continence, transferring, going to the toilet, dressing and bathing. Increases in score from one to six indicate progressively worsening functional impairment.

Table 1   Sex distribution of study population and patients with rheumatoid arthritis or taking corticosteroids

	Cases		Controls	
	Male	Female	Male	Female
Number	60	240	120	480
Rheumatoid arthritis	1	13	2	12
Corticosteroid use	1	15	1	12

Table 2   Hip fracture risk in patients with rheumatoid arthritis and those taking corticosteroids

Risk factor	Sex	Odds ratio			
		Unadjusted (95% CI)	p	Adjusted* (95% CI)	p
Rheumatoid arthritis	Men	1·0 (0·1 to 11·0)	1·00	1·0 (0·1 to 11·0)	1·00
	Women	2·4 (1·0 to 5·4)	0·04	2·1 (0·9 to 5·0)	0·09
	Both	2·1 (1·0 to 4·7)	0·06	1·9 (0·9 to 4·3)	0·11
Corticosteroid use	Men	2·0 (0·1 to 32·0)	0·63	2·0 (0·1 to 32·0)	0·63
	Women	2·8 (1·2 to 6·2)	0·01	2·5 (1·1 to 5·8)	0·03
	Both	2·7 (1·2 to 5·8)	0·01	2·5 (1·1 to 5·5)	0·02

*Odds ratio for fracture from rheumatoid arthritis, after adjusting for steroid use (and vice versa) in a multiple logistic regression model. CI = Confidence interval.

Table 3   Body build, functional impairment, lifestyle, and the risk of hip fracture

Risk factor	Category		Number of		Odds ratio (95% CI)	
			Cases	Controls		
Body mass index	M	F				
(kg/m²)	<20·4	<19·2	88	84	1·0	—
	20·4	19·2	67	94	0·6	(0·4 to 1·0)
	21·6	21·1	60	112	0·5	(0·3 to 0·8)
	23·2	22·9	40	128	0·3	(0·2 to 0·5)
	>24·9	>25·6	24	144	0·2	(0·1 to 0·3)
Functional impairment	1		157	420	1·0	—
(Katz ADL score)	2		77	124	1·9	(1·3 to 2·8)
	3		38	34	3·4	(2·0 to 5·8)
	4+		28	21	4·4	(2·3 to 8·4)
Cigarette smoking	Ever v never		145	223	1·7	(1·2 to 2·3)
Alcohol consumption	Occasional/abstainer		163	328	1·0	—
	Light		108	205	1·3	(1·0 to 1·8)
	Moderate/heavy		28	12	7·5	(3·3 to 16·8)

CI = Confidence interval.

Table 4   Hip fracture risk in patients with rheumatoid arthritis, after sequential adjustment for body mass index, cigarette smoking, alcohol consumption, and functional impairment

Risk factor	Other variables in model	Odds ratio (95% CI)	p
Rheumatoid arthritis	None	2·1 (1·0 to 4·7)	0·06
	BMI, smoking, alcohol	1·9 (0·8 to 4·8)	0·12
	BMI, smoking, alcohol, ADL	1·3 (0·5 to 3·5)	0·78

CI = Confidence interval; BMI = body mass index; ADL = assessment of activities of daily living.

Table 5   Hip fracture risk in patients using corticosteroids after sequential adjustment for body mass index, cigarette smoking, alcohol consumption, and functional impairment

Risk factor	Other variables in model	Odds ratio (95% CI)	p
Corticosteroid use	None	2·7 (1·2 to 5·8)	0·01
	BMI, smoking, alcohol	2·5 (1·1 to 5·9)	0·04
	BMI, smoking, alcohol, ADL	2·1 (0·9 to 5·2)	0·06

CI = Confidence interval; BMI = body mass index; ADL = assessment of activities of daily living.

Comparisons between cases and controls were by conditional logistic regression for matched sets.[19] In case control studies, this analysis permits estimation of odds ratios as measures of association, which may be interpreted as relative risks.

Results

The ages of the cases ranged from 50 to 99 (median 79) years. To obtain the required 600 controls it was necessary to approach 889 subjects. The reasons for the incomplete response were death or change of address (73), failure of mental test (65), and refusal (151). Fourteen cases (4·7%) and 14 controls (2·3%) were identified who had rheumatoid arthritis (table 1); 25 of these 28 (89%) were women. The mean age of cases with hip fracture was 79 (range 50–99) years, that of cases with rheumatoid arthritis was 76 (60–87) years, while that of arthritic controls was 77 (66–90) years. The overall prevalence of corticosteroid use in the study sample was 3·2%. Of the 29 individuals who were taking corticosteroids, 16 were cases and 13 were controls. In six of the 29 receiving steroids, rheumatoid arthritis was documented. In the remaining 23, the major reasons for steroid use were chronic obstructive airways disease and polymyalgia rheumatica.

Table 2 shows that the unadjusted risk (odds ratio) of hip fracture in patients with rheumatoid arthritis was 2·1 (95% confidence interval (CI) 1·0 to 4·7; p = 0·06); that in subjects who were receiving steroids was 2·7 (95% CI 1·2 to 5·8; p = 0·01). Table 2 also shows that when these risk estimates were mutually adjusted in a logistic regression model, it was apparent that the effects of rheumatoid arthritis and steroid use on hip fracture were, to a large extent, independent of each other. In a separate stratified analysis, those taking steroids but who did not have rheumatoid arthritis had a fracture risk of 2·8 (95% CI 1·2 to 6·5), while patients with rheumatoid arthritis who did not use steroids had an odds ratio for hip fracture of 2·2 (95% CI 0·9 to 5·1). There was little evidence for a multiplicative effect between steroid use and rheumatoid arthritis: the odds ratio in patients with both exposures was only 2·9 (95% CI 0·6 to 15·0).

Table 3 shows the distribution among cases and controls of four other variables found to be significantly (p < 0·05) associated with fracture risk. Risk declined progressively with increasing body mass index and increased with increasing functional impairment. It was also increased by cigarette smoking and alcohol consumption. Tables 4 and 5 show the risk of hip fracture with rheumatoid arthritis and steroid use, after sequential adjustment for body mass index, cigarette smoking, alcohol consumption, and functional impairment. The excess risk attributable to steroid therapy appeared little changed by adjustment for these potentially confounding variables, while that for rheumatoid arthritis was markedly reduced by adjusting for functional impairment. These

changes in odds ratio, however, did not attain statistical significance, perhaps because of the relatively low prevalence of both rheumatoid arthritis and steroid consumption in the study sample as a whole.

Discussion

The results of this study suggest that the risk of hip fracture is increased in patients with rheumatoid arthritis and in those who take corticosteroids. For both these exposures, the risk of hip fracture is approximately doubled, and the effects of each exposure appear to be largely independent of the other. Among patients with rheumatoid arthritis, the increased risk of hip fracture appears to be attributable predominantly to the functional impairment associated with the disease. However, the risk increase in those taking corticosteroids was little changed by adjusting for body mass index, cigarette smoking, alcohol consumption, and functional status.

Although many studies have examined changes in bone density among patients with rheumatoid arthritis,[1-12] there have been relatively few controlled studies investigating the clinically more relevant end point of fracture.[13 14] In the only previous population based study to address specifically the issue of hip fracture risk in rheumatoid arthritis, 388 women from the northern United States who initially developed rheumatoid arthritis during the period 1950–74, were followed subsequently for 4902 person years.[13] Twenty nine of them sustained hip fractures, and when this experience was compared with the expected incidence rate of hip fracture in that population, a relative risk of 1·5 was obtained. As with our own study, there was limited power to assess the contributions of various risk factors to this increase in risk, but a multivariate analysis suggested that ageing, impaired ambulation and thinness acted as independent risk factors. Although those receiving steroids had a greater risk of hip fracture (relative risk = 2·15) than others (relative risk = 1·40), these estimates were not significantly different. Given the differences in population samples and study design, these findings are very similar to our own. It is possible that, in our study, exclusion of subjects with dementia (a group likely to manifest a concentration of comorbidity) permitted better delineation of the independent contributions of rheumatoid arthritis and steroid use, to hip fracture risk. The excess of hip fracture in our study is also remarkably close to that observed for vertebral fracture in patients with rheumatoid arthritis.[20]

There are many difficulties in studying the association between disorders such as rheumatoid arthritis and fracture risk. When studies are population based, the prevalance of rheumatoid arthritis tends to be relatively low, and statistical power is correspondingly limited. Furthermore, there is no widely accepted method for the identification of those with rheumatoid arthritis in population studies. Through the use of a screening question enquiring about physician diagnosed rheumatoid arthritis, we are likely to have imposed a relatively specific but insensitive diagnostic threshold.[21] The recording of ARA criteria in hospital and general practice case records, however, is likely to be incomplete, and hospital records were only available for the cases. When the additional five self reporting cases were included in the analysis, the odds ratio for rheumatoid arthritis increased from 2·1 to 2·7. The correspondence of these estimates with the previously performed North American retrospective cohort study[13] supports their validity.

Rheumatoid arthritis is a systemic disease which results in joint inflammation and associated joint destruction. The release of cytokines by inflamed synovium mediates juxta-articular osteopenia which is most marked in the appendicular skeleton.[7] Studies of axial bone density in patients with rheumatoid arthritis are rather less consistent.[6 9-12] Some studies have reported that lumbar spine or femoral neck bone mineral density are reduced significantly in patients with rheumatoid arthritis who have not been treated with corticosteroids.[6 9 10] Others, however, have documented normal bone density values in women with the disorder.[11 12] In the only detailed study incorporating sufficient numbers of men, both steroid treated and non-steroid treated men with rheumatoid arthritis had low femoral neck bone density values.[10] An increase in hip fracture risk among patients with rheumatoid arthritis might also be mediated through an increased risk of falling. Although cigarette smoking has not been clearly linked to falls in the elderly, functional impairment, heavy alcohol consumption, and low body mass have all been documented as risk factors for falling in epidemiological studies.[22 23]

Data on the influence of corticosteroids on bone density are numerous.[24] There is consistent evidence that use of these agents is associated with a reduction in bone density, particularly in areas which contain a large proportion of trabecular bone. Remarkably, however, there are no published estimates from population based studies of the increase in hip fracture risk associated with steroid use. The median dose of prednisolone taken by the patients reporting steroid use in our study was 7·5 mg daily. We were unable to obtain reliable estimates of the duration of use, or of previous use in individuals who were not current users. Our data suggest that steroid therapy is associated with a significant increase in hip fracture risk, and that this effect is independent of other risk factors for osteoporosis or falling. The independence of effects attributable to steroid use and rheumatoid arthritis is not surprising given the small number of cases in whom both factors were operating, and studies with greater statistical power are required to explore any potential interaction between these two exposures. The apparent independence of the two risk factors might also have resulted from the fact that current steroid use (rather than use ever) was ascertained. It is interesting,

however, that steroid use in individuals with rheumatoid arthritis did not serve to increase markedly the overall risk of hip fracture. This influence of steroids on hip fracture risk in our study was in marked contrast to that previously reported on vertebral fracture risk. Spector *et al*[20] examined the prevalence of vertebral deformities in 191 postmenopausal women with rheumatoid arthritis; five (28%) of those with vertebral fractures had received steroids, compared with 46 (35%) of those without fractures. Several case series, however, document prevalence rates of vertebral deformity which are considerably greater than expected among patients taking cortico-steroids.[25-28]

In conclusion, our data provide evidence that the risk of hip fracture is approximately doubled among patients who suffer from rheumatoid arthritis, and among those taking steroids. The risk increases attributable to each of these factors are, to some extent, independent of each other. In the case of rheumatoid arthritis, the major contributors to excess hip fracture risk appear to be thinness and functional impairment. Steroid use, however, does not appear to be confounded by these two variables. Clinicians should be aware of the association between rheumatoid arthritis, steroid therapy, and this most catastrophic outcome of bone loss. The investigation of measures to retard bone loss in the femoral neck should be evaluated urgently in patients with rheumatoid arthritis, to try and reduce the incidence of hip fracture.

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