Calcium absorption in rheumatoid arthritis

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SUMMARY Calcium absorption, assessed by a double isotope method, was found to be impaired in postmenopausal women with rheumatoid arthritis of recent onset (mean 14.2 months) compared with controls. Circulating levels of 1,25-dihydroxyvitamin D (calcitriol) were higher than in controls, suggesting a primary malabsorption of calcium in these patients. The reduction in calcium absorption correlated with several measures of disease activity, suggesting that the disease process was responsible for the intestinal defect, but an effect from non-steroidal anti-inflammatory agents cannot be excluded. A primary reduction in calcium absorption may increase the risk of osteoporosis in women with rheumatoid arthritis.

Key words: calcium metabolism, malabsorption, anti-inflammatory drugs.

A generalised disturbance of skeletal metabolism has been suggested to occur in rheumatoid arthritis (RA) leading to osteoporosis.¹⁻³ Calcium homeostasis is regulated in part by changes in intestinal absorption of calcium, yet there have been few studies of calcium absorption in RA, and these have yielded conflicting results. Olhagen *et al.*⁴ found calcium absorption was reduced, whereas Kennedy *et al.*⁵ found it to be increased. Problems with methodology and the concomitant use of oral corticosteroids in some patients makes interpretation of both studies difficult.

In the present study we have measured calcium absorption in patients with RA and in a group of age and sex matched controls. Since among RA patients who have not been treated with corticosteroids postmenopausal women are the group most at risk of developing osteoporosis,⁶ this study is concerned with predominantly postmenopausal women who had recently developed RA.

Patients and methods

SUBJECTS

Female patients attending two general rheumatology outpatient clinics who had developed sero-

positive classical or definite RA⁷ in the preceding three years and who were approaching the menopause or were postmenopausal were asked to participate; patients receiving oral corticosteroids were excluded.

Control subjects were volunteers, in good health and not taking drugs known to produce osteoporosis; two were taking non-steroidal anti-inflammatory drugs (NSAIDs) for minor degenerative joint disease. One control was subsequently excluded because she suffered from Parkinson's disease, and it was thought this might affect gut transit time. Details of patients and controls are shown in Table 1. Informed consent was obtained from each subject and the study received Ethical Committee approval (EC No 924).

A questionnaire prepared by the Department of Dietetics at Northwick Park Hospital was used to obtain a history of calcium intake. An assessment was made at the time of the calcium absorption test and repeated three months later to assess reproducibility; the dietary calcium intake was calculated as the average of these two values.

Disease activity was assessed before the calcium absorption test by the following: Ritchie articular index;⁸ joint count (number of active joints); duration of early morning stiffness; grip strength (mean of three recordings, dominant hand); erythrocyte sedimentation rate; C-reactive protein (CRP).

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Table 1 Clinical details of patients and controls (range given in parentheses)

Clinical details	Rheumatoid arthritis	Controls
Mean age (years)	n=20 55.8 (37-67)	n=14 56.4 (41-69)
Mean disease duration (months)	14.2 (2-31)	—
Number postmenopausal	15	11
Mean number years postmenopausal	10.4 (1.5-22)	8.1 (1.0-23)
Number on NSAIDs	19	2
Number on disease modifying agents	11	—

LABORATORY STUDIES

Calcium absorption was studied in patients and controls by the method of Wootton and Reeve.⁹ Subjects on their usual diet and medication were fasted from midnight until three hours after the start of the test. A 444-555 kBq dose of ⁴⁷CaCl₂ was used as the oral tracer with 2.5 mmol of calcium chloride as carrier. A 111-185 kBq dose of ⁸⁵SrCl₂ was used as the intravenous tracer. The effective dose equivalent from the procedure was 0.76-0.95 mSv for the oral tracer and 0.10-0.16 mSv for the intravenous tracer. From the plasma activity-time curve for each tracer the spectrum of transit times from the gut lumen to plasma was derived by deconvolution. The fraction of dose absorbed (FA), maximum absorption rate (MAR), and mean absorption rate (AR) were calculated from the curve describing the spectrum of transit times. Blood samples were taken before the start of the calcium absorption study with the subjects fasting for determination of plasma calcium, albumin, and creatinine. Calcium values were corrected by adding or subtracting 0.02 mmol/l for every 1 g/l the albumin was below or above 40 g/l. A fasting early morning urine specimen was collected on the day of the calcium absorption study for determination of calcium and creatinine.

25-Hydroxyvitamin D (calcidiol) levels were measured by a competitive protein binding assay.¹⁰ The sensitivity of this method was 50 pg per tube with intra-assay and interassay variation of 10.1 and 13.2% respectively. The 1,25-dihydroxyvitamin D (calcitriol) levels were measured by a radioreceptor assay with an intestinal receptor preparation and by a modified extraction and separation procedure by high performance liquid chromatography.¹¹ Intra-assay and interassay variation were less than 10%, and the detection limit was less than 5 ng/l.

Bone density in the wrist was measured with

an 'Isotom' purpose-built computed tomography densitometer employing a ¹²⁵I source (29 keV, 7.4-18.5 GBq) as previously described.¹² Trabecular bone density was measured in the distal radius at 8-10% of the distance between the ulnar styloid and olecranon as the mean linear attenuation coefficient of the inner 50% of the bone cross section. Cortical bone mass was measured in the midshaft at one third of the distance between the ulnar styloid and olecranon as total absorption, calculated as mean linear attenuation coefficient of the whole cross section multiplied by cross-sectional area. The radiation dose with this method is approximately 0.02 mSv per measurement at the measurement site. Bone density in the lumbar spine was measured as the mean bone mineral content of the second to fourth lumbar vertebrae (L2-L4) by a Novo 22A dual photon absorptiometer employing a ¹⁵³Gd source (44 keV, 100 keV, 40 GBq) as previously described.¹³ The radiation dose with this method is: skin dose over L3 0.10 mGy; ovary dose <0.02 mGy (1 Gy=100 rads).

Unpaired Student's *t* tests were used to determine significance levels of differences between means in the two groups, and log transformation was used to normalise the vitamin D data. Simple correlation analyses were also performed.

Results

There was no significant difference in mean values of plasma calcium and plasma creatinine between the two groups. Correction of calcium values for the albumin did not alter this result.

The results of the calcium absorption studies and bone density measurements are shown in Table 2. Fractional absorption was significantly reduced in patients compared with controls; other measures of calcium absorption were also reduced but failed to reach statistical significance. Two indexes of calcium absorption correlated significantly with clinical indexes of disease activity in RA patients: MAR correlated with grip strength ($r = +0.49$, $p < 0.01$) and Ritchie index ($r = -0.47$, $p < 0.01$), and AR correlated with the Ritchie index ($r = -0.64$, $p < 0.001$). Indexes of calcium absorption did not correlate significantly with laboratory measures of disease activity. FA did not correlate significantly with any index of disease activity. The levels of calcitriol were increased significantly in RA patients compared with controls. No significant correlation was found between calcitriol and calcium absorption measured by any index. The coefficient of variation between diet histories was 17.8%. There was no significant difference in calcium intake between RA patients and controls.

Table 2 Results of calcium absorption studies and bone density measurements (mean $\pm$ SD)

	Rheumatoid arthritis	Controls	Significance†
Fractional absorption	53.4 $\pm$ 10.1	62.7 $\pm$ 12.1	p<0.025
Maximum absorption rate	26.1 $\pm$ 7.8	28.5 $\pm$ 5.5	NS
Mean absorption rate	17.9 $\pm$ 4.3	19.6 $\pm$ 4.6	NS
Dietary Ca intake (mmol/day)	17.4 $\pm$ 8.0	20.9 $\pm$ 6.6	NS
Urinary calcium/creatinine ratio (fasting early morning)	0.38 $\pm$ 0.21	0.37 $\pm$ 0.13	NS
Calcidiol (μ g/l)	13.1	15.2	NS
range*	8.8–19.5	10.8–21.3	
Calcitriol (ng/l)	30.6	16.1	p<0.01
range*	23.1–40.4	11.2–23.1	
Trabecular bone density (distal radius, cm ⁻¹)	0.66 $\pm$ 0.13	0.74 $\pm$ 0.22	NS
Total absorption (midshaft, cm)	2.41 $\pm$ 0.41	2.50 $\pm$ 0.31	NS
Mean lumbar bone mineral content (L2–L4, g/cm)	3.52 $\pm$ 0.46	3.44 $\pm$ 0.68	NS

*Range=antilog (log mean $\pm$ 2 log SE).

†Unpaired Student's *t* tests (two-tailed); NS=not significant.

Discussion

Published studies of calcium absorption in RA have yielded conflicting results. Olhagen *et al.*⁴ measured the retention of oral ⁴⁷Ca by whole body counting in eight patients with RA and generalised osteopenia, of whom three were receiving corticosteroids. A moderate reduction in retention was found at one and two weeks compared with controls, suggesting impaired calcium absorption. However, this method is an indirect measure of calcium absorption, since whole body retention is determined not only by intestinal absorption but also by bone accretion rates and endogenous faecal excretion of calcium.⁹

Kennedy *et al.*⁵ studied calcium absorption by a single tracer method in 24 patients with RA, of whom 10 were receiving corticosteroids. These workers measured plasma ⁴⁷Ca concentrations two hours after an oral dose of ⁴⁷Ca and found significantly raised levels in non-corticosteroid treated patients compared with controls and even higher concentrations in corticosteroid treated patients. Since corticosteroids are known to impair calcium absorption, these results are surprising. However, plasma radiocalcium concentrations measured two hours after oral administration provide only an index of calcium absorption. Although the method correlates well with absorption as measured by double isotope techniques in the majority of cases,¹⁴ it becomes inaccurate if absorption is delayed or the rate of extraction of calcium from the blood stream is abnormal. Variations in intestinal transit time, urinary calcium excretion, endogenous faecal calcium output, and accretion may all significantly influence the result.⁹

In our study with a double isotope technique we

found a moderate but significant reduction in fractional absorption in RA. The finding of higher mean calcitriol levels in the RA patients suggests primary malabsorption rather than impairment of absorption secondary to altered calcium metabolism.

Dyer *et al.*¹⁵ have suggested that RA may be associated with gastrointestinal malabsorption; these authors found abnormal faecal fats in six out of 15 and low D-xylose absorption in four out of 28 patients with RA; jejunal biopsies in 13 patients were normal. In general, pathological changes in the gastrointestinal tract are uncommon in RA but may occur in association with Sjögren's syndrome or rheumatoid vasculitis.¹⁶ In our study only one patient had evidence of Sjögren's syndrome, and no patient had clinical features suggesting vasculitis.

Alternatively, calcium malabsorption might be drug induced. All but one of our patients were receiving some form of NSAID up to the day before the study, and the effect of these drugs on calcium absorption is unknown, but they have been found to alter intestinal permeability.¹⁷ Bird *et al.*¹⁸ found that calcitriol levels were normal in patients with longstanding RA when compared with patients with osteoarthritis; as most of the patients in both groups in this study were taking NSAIDs an effect of these drugs might have been missed. A wide variety of NSAIDs were being taken in the present study and it was not possible to relate reductions in FA to individual drugs, but there did not appear to be a relationship between low FA and therapy with long half life NSAIDs. Similarly, impaired calcium absorption was not related to the use of disease modifying drugs.

Cross-sectional bone density studies in our

patients showed no significant differences in mean values when compared with controls. Since the RA in these patients was of recent onset, it is possible that significant changes in bone density might not have had time to develop. Longitudinal studies of bone density trends in these patients are currently in progress to determine whether the reductions in calcium absorption are related to the later development of osteoporosis.

In conclusion, calcium absorption appears to be reduced in RA due to a primary malabsorptive process; the mechanism is uncertain. Rates of calcium absorption correlated with several measures of disease activity, but an effect of NSAIDs cannot be excluded. Impaired calcium absorption will increase the risk of osteoporosis in RA.

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