Whole body elemental composition during drug treatment of rheumatoid arthritis: a preliminary study

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SUMMARY Thirty-two female patients with rheumatoid arthritis were divided into 3 groups and treated for 6 months with prednisolone, depot tetracosactrin, or indomethacin. Their whole body content of calcium, phosphorus, and nitrogen was measured before and after 3 and 6 months' treatment by in-vivo neutron activation analysis. No significant changes in these body elements were observed as a result of the treatments. The average amounts of calcium, phosphorus, and nitrogen were lower than normal in these patients, a finding consistent with the frequent observation of osteoporosis and muscle wasting in rheumatoid arthritis.

Osteoporosis is a common complication of rheumatoid arthritis (Duncan, 1972), and corticosteroid therapy has been implicated as an aggravating factor in producing bone loss in this disease (Mueller, 1976; Kennedy and Lindsay, 1977). Recent evidence (Kennedy *et al.*, 1975, 1976) suggests that bone loss is not due simply to disuse associated with this chronic disease but also to an active process involving major disturbances in calcium metabolism. The nature of this bone loss is of therapeutic importance, but no less important are the rate of bone loss and factors affecting it.

Radiographic and densitometric methods of quantifying bone loss are generally unsatisfactory (Simon, 1965; Aloia *et al.*, 1975). Changes in body content can be studied by metabolic balance methods over short periods of time, but it is not practicable to assess the longer-term changes in body composition by such methods. However, total body in-vivo neutron activation analysis (TBIVNAA) is a technique by which the content of elements in the whole body are estimated. Comparison of such measurements may therefore permit changes in body composition to be detected whatever the period of time during which the changes take place. We

have used this technique to examine the effects of 2 forms of corticosteroid treatment on the whole body content of calcium, phosphorus, and nitrogen over a period of 6 months. Patients treated with a non-steroid drug (indomethacin) were also studied for comparison.

Patients

Thirty-two female patients suffering from definite or classical rheumatoid arthritis (Ropes *et al.*, 1959) were studied. Their ages ranged from 40 to 70 years (mean 54). Each patient was given 1 of 3 treatments: (A) Indomethacin 25 mg orally 3 times daily (12 patients); (B) depot teracosactrin 2 mg by intramuscular injection, twice weekly (10 patients); (C) prednisolone 5 mg orally twice daily (10 patients). No other drug was given during the study period of 6 months. At the end of this time corticosteroid therapy was withdrawn without any adverse effects.

Each patient gave her consent after a full explanation of the implications. The Ethical Committee of Glasgow Royal Infirmary approved the study.

Methods

Measurements of whole body calcium, phosphorus, and nitrogen were made 1 day before starting treatment and again 3 and 6 months later. For each

measurement the patient's natural body radioactivity was measured by means of a shadow-shield, scanning-bed whole-body counter (Boddy *et al.*, 1975). The patient was then irradiated while lying on a motor-driven bed which passed between two 14 MeV sealed-tube neutron generators, mounted one above and one below the patient in a concrete shield (Boddy *et al.*, 1973). The radioactivity induced in the body elements by the irradiation was then measured by the whole-body counter. The counts obtained from each patient were expressed as grams of each element with the use of calibration factors obtained by irradiating a series of water filled anthropomorphic phantoms. Each phantom contained one of the appropriate elements; the procedure used was similar to that described by Williams *et al.* (1978). The radiation dose to the whole body at the body surface was 1 rem, which is comparable to that for many medical x-ray investigations.

Results

Clinical and laboratory findings in the patients are shown in Table 1. The 3 treatment groups were similar in age, rheumatoid factor titre (Ball, 1952), erythrocyte sedimentation rate (Westergren), and functional capacity (Steinbrocker *et al.*, 1949). However, in group B the average duration of disease

was less than in the other 2 groups. Articular index and grip strength were comparable for the 3 groups initially and, apart from grip strength in the indomethacin-treated group, improved during treatment.

The results of the TBIVNAA measurements of calcium, phosphorus, and nitrogen were expressed as ratios of the 3 and 6 months' to the initial measurements (Table 2). Generally, no significant changes in body content of the 3 elements were observed as a result of each treatment, nor were there any significant differences between each treated group. There was 1 exception: in the indomethacin-treated group, whole body phosphorus was significantly higher (by 3%) at 3 months than its initial value ($P < 0.05$, *t* test and Wilcoxon signed rank sum test). However, the 6-month result was not significantly different from the initial result.

Since a large number of statistical tests were performed on the data, spurious significant results (at the 5% level) were to be expected to 5% of tests. The number of comparisons was therefore reduced by grouping the data, combining the results for calcium and phosphorus, representing bone mineral elements, and combining results for patients treated with tetracosactrin and prednisolone (both corticosteroids). No differences between treatments occurred during treatment significant at the 5% level by tests were then observed.

Table 1 Clinical and laboratory indices for the 3 groups of patients at the start up of the study (mean $\pm$ SD)

Treatment group	Number	Age (yr)	Duration of disease	Rheumatoid factor titre ¹	ESR (mm/h)	*Articular index	*Grip strength	Functional capacity
A. Indomethacin	12	57 $\pm$ 6.6	9.5 $\pm$ 4.8	120	45 $\pm$ 31	(a) 24.6 $\pm$ 3.2 (b) 15.0 $\pm$ 2.7 (c) 11.6 $\pm$ 2.5	120 $\pm$ 40 126 $\pm$ 44 122 $\pm$ 41	2.07 $\pm$ 0.70
B. Tetracosactrin	10	52 $\pm$ 10	3.8 $\pm$ 2.6	242	49 $\pm$ 28	(a) 28.2 $\pm$ 5.1 (b) 11.4 $\pm$ 4.2 (c) 9.5 $\pm$ 3.5	87 $\pm$ 34 107 $\pm$ 39 111 $\pm$ 40	2.50 $\pm$ 0.91
C. Prednisolone	10	53 $\pm$ 7.5	11.0 $\pm$ 5.0	275	48 $\pm$ 24	(a) 30.0 $\pm$ 4.0 (b) 9.2 $\pm$ 2.2 (c) 9.0 $\pm$ 2.2	114 $\pm$ 30 121 $\pm$ 33 134 $\pm$ 42	2.40 $\pm$ 0.87

*These results were obtained after (a) 0, (b) 3, and (c) 6 months' treatment. ¹Reciprocal of titre.

Table 2 Relative amounts of whole body elements after 0, 3, and 6 months' treatment

Treatment	Months	Calcium Mean	SEM	Phosphorus Mean	SEM	Nitrogen Mean	SEM	Body weight Mean	SEM
A. Indomethacin	0	1.000	—	1.000	—	1.000	—	1.000	—
	3	1.000	0.026	1.031	0.012	1.002	0.031	0.992	0.008
	6	1.021	0.024	1.009	0.017	0.994	0.029	0.999	0.012
B. Depot Tetracosactrin	0	1.000	—	1.000	—	1.000	—	1.000	—
	3	1.001	0.047	1.008	0.012	1.012	0.030	1.087	0.029
	6	1.053	0.050	0.998	0.011	0.996	0.039	1.125	0.027
C. Prednisolone	0	1.000	—	1.000	—	1.000	—	1.000	—
	3	1.030	0.031	1.027	0.018	1.004	0.029	1.046	0.022
	6	0.969	0.019	1.016	0.021	1.001	0.026	1.052	0.019

SEM = standard error of mean.

Table 3 Details of patients whose whole body elemental compositions were compared

Patient group	Number	Height (m)		Weight (kg)		Age (yr)	
		Mean	Range	Mean	Range	Mean	Range
Rheumatoid arthritis	32	1.58	1.44-1.72	58.7	39-92	54	40-70
Hypertension	23	1.59	1.48-1.67	64.1	44-80	52	40-70

Table 4 Comparison of elemental contents (in grams) of patients with rheumatoid arthritis and with hypertension

Patient group	Calcium		Phosphorus		Nitrogen	
	Mean	SD	Mean	SD	Mean	SD
Rheumatoid arthritis (RA)	660	124	412	71	1120	144
Hypertension (H)	803	100	462	58	1280	156
Ratio: RA/H	0.82		0.89		0.87	
Significance level of difference	P<0.001		P<0.01		P<0.001	

The measurements of whole body elements in the patients before treatment were compared with those which would be expected in subjects not suffering from rheumatoid arthritis. The comparison was made with measurements on 23 females suffering from hypertension from various causes who were examined in another investigation (Boddy *et al.*, 1978). We have no reason to suppose that such patients would have abnormal contents of calcium, phosphorus, or nitrogen, and the average amount of calcium was similar to that predicted for normal persons of similar stature by Ellis and Cohn, (1975). The 2 groups were well matched for height, weight, and age (Table 3). The patients with rheumatoid arthritis had significantly less calcium, phosphorus, and nitrogen than those with hypertension (Table 4).

Discussion

In this study of patients with rheumatoid arthritis no significant changes in calcium and phosphorus, the major constituents of bone mineral, were seen. Since the development of osteoporosis is often associated with loss of bone of only a few percent per year (Dent, 1969), changes would have been detectable in 6 months only if treatment substantially accelerated the loss. Measurements over a longer period may be more revealing.

In the patients treated with prednisolone and tetracosactrin there was on average an increase in body weight, whereas indomethacin-treated patients maintained constant weight. In patients whose body weight increased greatly an increase in body nitrogen was also observed, although by a smaller percentage. There may therefore be some increase in lean body mass resulting from amelioration of the disease,

though in other clinical contexts these drugs have a catabolic effect. Possibly the beneficial anti-inflammatory properties of corticosteroids outweighed the catabolic effects, though this hypothesis conflicts with the findings of Sprague (1950) of persistent protein catabolism in patients with rheumatoid arthritis treated with corticosteroids. However, most of the weight gain was probably due to increased body fat and water retention (Ernest, 1967).

The deficits in calcium and phosphorus, of 18% and 11% respectively, compared to the amounts in the patients with hypertension, are similar to the deficit of 18% found by Cohn *et al.* (1974) in females with osteoporosis. Loss of bone mineral is recognised as a common feature of rheumatoid arthritis. The association of pain and disease (Duncan, 1972) might also be expected to result in a diminution of muscle mass. This could explain why the average nitrogen content of these patients was 13% less than those with hypertension.

Two conclusions have been drawn from this study. First, patients suffering from rheumatoid arthritis have relatively low contents of calcium, phosphorus, and nitrogen. Secondly, the fact that changes in these elements were not detected during 6 months' treatment with corticosteroids suggests that no dramatic changes took place (an average change of about 7% or more would have been detected), and that if there were changes in the elements measured the period of the study was too short to have detected them. Nevertheless, the technique of TBIVNAA is well suited to longer-term studies of this nature.

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