Osteoporosis in the rheumatoid hand — the effects of treatment with D-penicillamine and oral gold salts

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Summary

Osteoporosis is a common and important feature of rheumatoid disease which can be further influenced by the treatment administered. D-penicillamine, a lathyritic agent, can also theoretically hasten the osteoporotic process through its effect on collagen metabolism. In the present study the effects of the long-term second-line drugs D-penicillamine and oral gold (Auranofin) on bone density are presented. All the patients studied lost bone mineral over the 3-year period, but continuous D-penicillamine therapy for 1 year reversed this trend. Oral gold did not have the same effect.

Measurements of bone density are an accurate indirect measurement of hand function, and there is a good correlation between hand function and the progress of osteoporosis. It is therefore suggested that treatment with D-penicillamine reverses the tendency to lose bone mineral improving synovitis, thus leading to improved hand function.

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Osteoporosis is a common and important complication of rheumatoid disease and can be peri-articular or generalized.[1,2] Various techniques have been used to study osteoporosis in rheumatoid disease,[3] and controlled studies have shown that bone mass is reduced in the femur and clavicle, suggesting that osteoporosis is not purely a localized condition caused by joint destruction. It has been difficult to show a relationship between the degree of osteoporosis and the activity of the rheumatoid process. It is, however, clear that the degree of osteoporosis does depend on the duration of the rheumatoid disease.[3] It is not certain to what extent the different possible causes of osteoporosis are involved in rheumatoid disease, but immobilization, dietary deficiency, malabsorption and possibly liver disease have been implicated. It has been suggested that patients with rheumatoid disease who receive corticosteroids are more likely to develop osteoporosis than patients receiving them for bronchial asthma or Cushing's syndrome; this may be because the joint disease leads to a mobility problem.

Radiological evaluation of osteoporosis is difficult, and other methods of evaluating bone status have been developed. These include quantified radiological and photon absorption methods. X-ray densitometry has largely been replaced by X-ray morphometry in which measurements are made directly from the radiographs. In the present study X-ray morphometry, i.e. measurement of the metacarpal index of Barnett and Nordin,[4] has been used to determine the effect of the long-term agent D-penicillamine or oral gold salts (Auranofin) on the progression of osteoporosis in the metacarpal bones.

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Patients and methods

A metacarpal index of osteoporosis was determined using standard posterior-anterior radiography of the hands. The latter were read blind and in a randomized order in an effort to avoid bias. The outside (D) and inside (d) diameters of the second metacarpal bone of the right hand were measured at their midpoint with a Vernier caliper (accurate to 0,01 mm) (Fig. 1). An area index (A1) was calculated from the formula $D^2 - d^2$, which gives an assessment of the cortical bone diameter ($\pi/2\ D^2 - d^2$). Exton-Smith *et al.*[5] have shown that this index correlates well with the ash weight of bone ($r = 0,85$). All the patients studied had classic or definite rheumatoid arthritis (RA) of at least 1 year's duration. Only patients in functional and anatomical classes 2 and 3 were studied. All patients who had previously undergone upper limb surgery were excluded from the study. Hand function was judged according to the patient's ability to perform daily activities, e.g. occupation, housework and personal care.

Control group. The control group consisted of 113 patients (25 males and 88 females) with RA. The mean ages were 46,4 years for the males and 50,6 years for the females, and the mean duration of disease was 6,1 years. Ten male and 26 female patients had each taken an average of 6 mg prednisolone per day for at least 2 years before the first radiograph was taken. Radiography was repeated after a mean period of 3 years. No patient in this group had ever received antimalarial drugs, gold, penicillamine or immunosuppressives.

D-penicillamine group. All the patients in both the penicillamine and gold salts groups had had active rheumatoid disease that was not responsive to the usual non-steroidal anti-inflammatory drugs for at least 9 months. This was characterized by persistent joint swelling, pain and stiffness and an increased erythrocyte sedimentation rate. Radiographs of 42 patients' hands were taken immediately before and after 1 year of continuous treatment with D-penicillamine (mean dose 750 mg/d). There were 13 male and 29 female patients, with a mean age of 49,8 years and mean duration of disease of 4,9 years (range 1 - 11 years). Twenty-one patients (7 males and 14 females) had also had radiographs taken of the hands some 3 years before D-penicillamine treatment was started.

Oral gold group. Seventeen patients (1 male and 16 females) were studied. The mean age was 53,7 years and the mean duration of disease 4,8 years (range 1 - 12 years). Radiographs were taken before oral gold treatment was started and again after 1 year of continuous treatment with 6 mg/d. No patient was taking corticosteroid drugs.

Hand function in the D-penicillamine and oral gold groups before treatment was started was similar, and was judged as previously described by the effects of the arthritis on daily living.

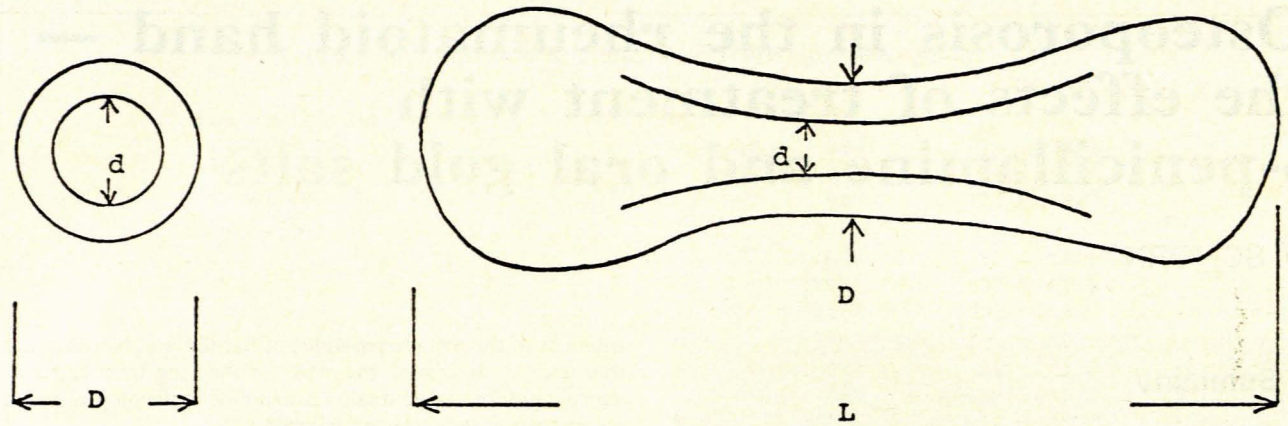


Fig. 1. Measurements used for calculation of the metacarpal index.

Results

Standardization

A series of 100 radiographs of the hands was used to determine the intra-observer error for the measurements. The measurements (D and d) of 100 metacarpal bones were taken and the procedure was repeated 3 days later. The difference between the readings (mean 2,4%) is quoted as the intra-observer error. This was not statistically significant ($P > 0,05$).

Progression of bone loss

Non-corticosteroid-treated patients. The AIs for the right second metacarpal bone calculated from radiographs taken a mean of 3 years apart were compared. Patients were subdivided into groups according to the duration of rheumatoid disease when the first radiograph was taken (0 - 5 years, 6 - 10 years, 11 -16 years, and > 16 years). The changes in the AIs for the different groups are shown in Table I. There was a progressive reduction in AI despite the fact that in all four groups the mean age had been similar when the first radiograph was taken. The difference between the AI for the 0 - 5-year group (61,7) and for the 6 - 10-year group (53,5) was statistically significant ($P <$ 0,0005), as was the difference between the 6 - 10-year group and the 11 - 15-year group; however, the latter was smaller ($P <$ 0,025). There was no difference between the 11 - 15-year and > 16-year groups. The mean reduction in AI became progressively smaller with a longer duration of disease. This is shown both by the absolute changes in AI and by the statistical analysis, where the P values became progressively greater. There was a statistically significant reduction in the AIs of all groups of patients during the observation period.

Corticosteroid-treated patients. Again the two hand radiographs were taken a mean of 3 years apart; all patients had been taking corticosteroids before the first radiograph was taken and had continued to use them during the observation period. Like the non-corticosteroid-treated patients they were further subdivided into groups according to the duration of the disease, and the results are shown in Table II. The groups are small in comparison with the non-corticosteroid-treated groups, but other than in the >16-year group the initial AI was not significantly lower in those patients who had had the disease for longer periods. Again there was a progressive reduction in AI over the 3-year observation period in all four groups. It was not possible to perform a separate statistical analysis comparing bone loss in male and female patients in the different groups because of the small numbers of males, but the males also showed a progressive reduction in AI over the observation period in all the groups.

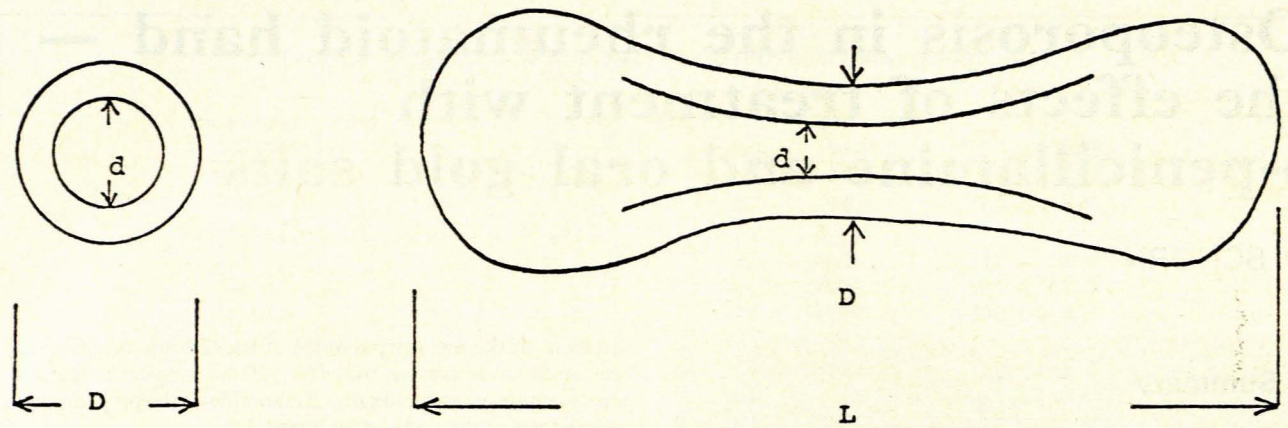
Effects of D-penicillamine. Twenty-one patients had radiographs taken a mean of 36 months before the start of D-penicillamine treatment and again after 1 year of continuous therapy (mean dose 750 mg/d). During this time the patients also received standard anti-inflammatory drugs when necessary. No patient had undergone hand, wrist or elbow surgery. There was a decrease in AI in the 3-year period before treatment was started from a mean of 62,2 (± 12,6) to 58,2 (± 15,4) ($P<0,025$) (paired t test). After a mean of 1 year of D-penicillamine therapy there was an increase in mean AI from 58,2 (± 15,4) to 63,5 (± 15,4) ($P < 0,01$) (paired t test). Follow-up radiographs were also

TABLE I. MEAN AI (± SD) IN FOUR GROUPS OF NON-CORTICOSTEROID-TREATED PATIENTS

	Duration of disease (yrs)			
	0 - 5	6 - 10	11 - 16	>16
Initial AI	**61,7 (± 12,3)**	**53,5 (± 10,9)**	**48 (± 10,8)**	**48,7 (± 12,3)**
Decrease in AI after 3 yrs	**5 (± 5,6)**	**3,1 (± 4,4)**	**2,2 (± 2,1)**	**2,7 (± 3,7)**
No. of patients	**34**	**20**	**10**	**13**

TABLE II. MEAN AI (± SD) IN FOUR GROUPS OF CORTICOSTEROID-TREATED PATIENTS

	Duration of disease (yrs)			
	0 - 5	6 - 10	11 - 16	>16
Initial AI	**57 (± 11,5)**	**60,3 (± 20,5)**	**61,3 (± 6,5)**	**51,7 (± 14)**
Decrease in AI after 3 yrs	**5,1 (± 4,2)**	**9,4 (± 9,5)**	**4,3 (± 6,2)**	**4,3 (± 2,3)**
No. of patients	**9**	**10**	**6**	**11**



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