THE LANCET

Vol 338 Saturday 12 October 1991 No 8772

ORIGINAL ARTICLES

Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis

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Fasting is an effective treatment for rheumatoid arthritis, but most patients relapse on reintroduction of food. The effect of fasting followed by one year of a vegetarian diet was assessed in a randomised, single-blind controlled trial.

27 patients were allocated to a four-week stay at a health farm. After an initial 7–10 day subtotal fast, they were put on an individually adjusted gluten-free vegan diet for 3·5 months. The food was then gradually changed to a lactovegetarian diet for the remainder of the study. A control group of 26 patients stayed for four weeks at a convalescent home, but ate an ordinary diet throughout the whole study period. After four weeks at the health farm the diet group showed a significant improvement in number of tender joints, Ritchie's articular index, number of swollen joints, pain score, duration of morning stiffness, grip strength, erythrocyte sedimentation rate, C-reactive protein, white blood cell count, and a health assessment questionnaire score. In the control group, only pain score improved significantly. The benefits in the diet group were still present after one year, and evaluation of the whole course showed significant advantages for the diet group in all measured indices.

This dietary regimen seems to be a useful supplement to conventional medical treatment of rheumatoid arthritis.

Lancet 1991; 338: 899–902.

Introduction

Most general practitioners and rheumatologists have encountered patients with rheumatoid arthritis who claim that their symptoms are alleviated by a special diet or by simple elimination of certain items from the usual diet. Such reports tend to be viewed with scepticism. Only a few arthritis patients have convincing "food allergy",[1-3] and clinical trials of "diet therapy" have yielded conflicting results.[4-7] Fasting, however, does reduce objective as well as subjective indices of disease activity in most patients with rheumatoid arthritis.[4,8,9]

We have evaluated the effect of a short fast followed by one year of individually adjusted vegetarian diet in patients with rheumatoid arthritis. The dietary regimen was the one used in a Norwegian health farm, slightly modified for the clinical trial.

Patients and methods

Patients

53 patients with classic or definite rheumatoid arthritis[10] in functional class II or III[11] (45 women and 8 men) were enrolled

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TABLE I—PATIENT CHARACTERISTICS AT ENTRY

—	Diet group n=27	Control group n=26
Age, yr		
Mean	53	56
Range	26–63	38–78
Sex		
M	3	5
F	24	21
Disease duration, yr		
Mean	6	8
Range	1–38	1–31
Functional category		
Class II	24	26
Class III	3	0
Rheumatoid factor (IgM)		
Positive	13	16
Negative	14	10
Current medication		
NSAID	16	17
Corticosteroids	5	5
Antimalarial drugs	0	3
Gold	3	1
Penicillamine	1	1
Sulphasalazine	0	1
Cytostatic drugs	2	2
None	3	2
*Allergy/intolerance**		
Food	13	10
Other types	6	9

*Patients' own reports.

between Jan 1, 1987, and Oct 1, 1989. They were recruited mainly through the outpatient department of the Oslo Sanitetsforenings Rheumatism Hospital, which receives patients from the whole of Norway. All had active disease, as defined by the presence of three of the following four criteria: ≥3 swollen joints; ≥6 tender joints; morning stiffness ≥45 min; erythrocyte sedimentation rate (ESR) ≥28 in the 1st hour. Further patient characteristics are given in table I.

Before inclusion, patients using slow-acting antirheumatic drugs (SAARDs) or cytostatic drugs had to have been on a stable dose for at least 3 months. Corticosteroid dosage was not to exceed 7·5 mg/day prednisone equivalent and the dose had to have been stable for 4 weeks before study entry. The dose of non-steroidal anti-inflammatory drugs (NSAIDs) likewise had to have been stable for at least 3 weeks. No change in the dosage of SAARDs, cytostatic drugs, or corticosteroids (by mouth or by intra-articular injection) was allowed during the study. If necessary, the dose of NSAIDs and analgesics could be changed. Patients were asked not to use omega-3 fatty acid supplements other than cod liver oil; the dose of this had to have been stable for 6 weeks before entry and was to be kept the same throughout the study period. Patients using selenium and vitamin E supplements were also to continue with the same dosage.

Design

The study was a 13-month prospective, single-blind, randomised trial, approved by the regional scientific ethics committee. By block randomisation,[12] with 6 patients in each block, 27 patients were allocated to a diet group and 26 patients to a control group. The patients started one of the treatment regimens as soon as possible after they had agreed to participate; in most instances, they were assembled in small groups who started the trial at the same time. The result of the randomisation was unknown to the patient until the first examination was completed.

The patients in the diet group began their four week stay at a health farm by fasting for 7–10 days. Dietary intake during the fast consisted of herbal teas, garlic, vegetable broth, decoction of potatoes and parsley, and juice extracts from carrots, beets, and celery. No fruit juices were allowed. The daily energy intake during the fast varied between 800 and 1260 kJ. After the fast the patients reintroduced a "new" food item every 2nd day. If they noticed an increase in pain, stiffness, or joint swelling within 2–48 h this item

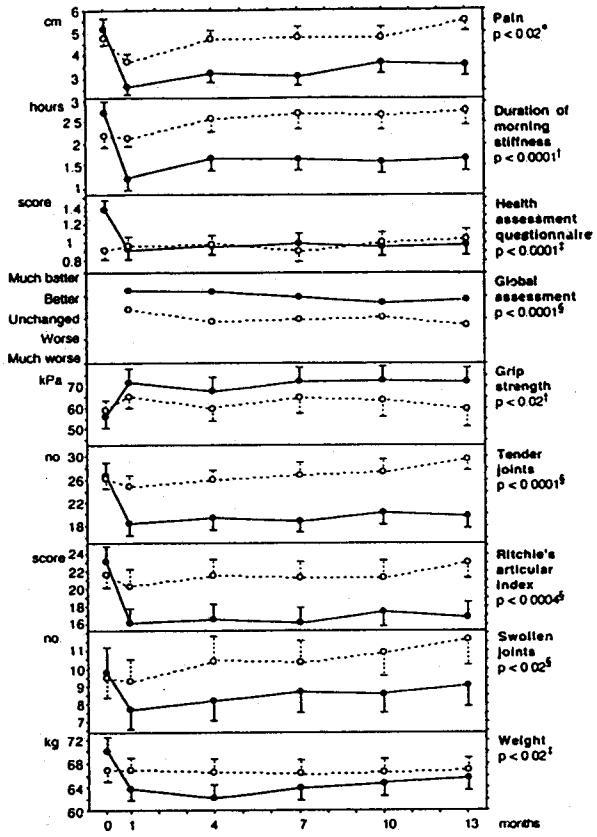

Fig 1—Clinical indices.

Mean and standard error of the mean for the diet group: ——●——. Mean and standard error of the mean for the control group: - - - -○- - - -. The standard errors of the mean for global assessment were too small to be depicted on the figure. The p values refer to overall group differences. *Unpaired t-test of the endpoint values. †Repeated measures ANOVA on the ranks. ‡ANACOVA. §Repeated measures ANOVA.

was omitted from the diet for at least 7 days. If symptoms were exacerbated on reintroduction of this food item, it was excluded from the diet for the rest of the study period. During the first 3·5 months the patients were asked not to eat food that contained gluten, meat, fish, eggs, dairy products, refined sugar, or citrus fruits. Salt, strong spices, and preservatives were avoided—likewise alcoholic beverages, tea, and coffee. After this period the patients were allowed to reintroduce milk, other dairy products, and gluten containing foods in the way described above. The patients who did not use cod liver oil supplemented the diet with vitamin D during the first 4 months.

At the health farm the patients, who were instructed by the staff and the dietitian (MH), kept a diary reporting all food and liquid intake. During the rest of the study period they recorded all food items reintroduced and any worsening of symptoms subsequent to reintroduction.

The patients in the control group had a four week stay at a convalescent home and were asked to eat ordinary mixed food throughout the study. At the convalescent home they kept a diary of their food intake and thereafter they made a detailed record of food intake one day a week (the day being varied). Both groups were offered physiotherapy three times a week during the stay at the health farm or convalescent home.

Clinical and dietary assessments

All clinical examinations were done by a single physician (J. K. K.), who did not know the group to which patients had been allocated (they were asked not to divulge it). Examinations were

TABLE II—DROP-OUTS

Time after recruitment		1st mo	4th mo	7th mo	10th mo
Drop-outs in diet group	Treatment related	1*	1†	3†	0
	Not treatment related	0	2‡	2§	1§
Drop-outs in control group	Treatment related	1†	3†	1†	2†
	Not treatment related	0	1§	0	1§

*Could not cope with the diet.
†Withdrawn due to flare-up of arthritis symptoms.
‡One of the patients withdrawn because of side-effects of auranofine; the other was offered total joint replacement.
§Withdrawn because they were offered total joint replacement.

done at baseline, after four weeks at the health farm/convalescent home, and thereafter every 3 months. The patients recorded their pain (10 cm visual analogue scale) and duration of morning stiffness; and, for grading of functional ability, they filled in a health assessment questionnaire.[13] At the second and subsequent clinical evaluations the patients recorded their overall global assessment compared with that at entry to the study (scored as much better, better, unchanged, worse, and much worse). Joint count included Ritchie's articular index,[14] the number of joints that were tender or painful on movement, and the number of swollen joints. Three determinations of grip strength were made for each hand with 'Vigorimeter' (Martin, Tuttlingen, Germany). Statistical calculations were made on the sum of the medians of both hands. At the clinical consultation neither patient nor physician had access to the results from earlier visits—except pain scores from the previous visit, which were shown to patients. At baseline all patients had hand, wrist, and forefoot radiographs taken and these were done again in patients who completed the study. The pairs of radiographs were compared as described by Larsen et al.[15]

Haemoglobin, ESR, platelet count, white blood cell count, C-reactive protein, and serum albumin were measured initially and at each clinical evaluation. Food intake was assessed before study entry, at the time of each clinical evaluation, and by telephone (once) between clinical evaluations. Intake was assessed from 24-hour recalls by use of household measurements. Energy and intake of nutrients were calculated by means of the FIBER software package based on the Norwegian food composition table.[16]

Statistical analysis

Within-group differences at fixed time points were tested by paired t-tests. However, for duration of morning stiffness, grip strength, and C-reactive protein the Wilcoxon signed-rank test was used, mainly because of the presence of outliers. Repeated measures ANOVA was used for testing overall group differences.[17] Because of significant baseline difference between the two groups with regard to the health assessment questionnaire score an analysis of covariance (ANACOVA) was done for this variable.[18] ANACOVA was also performed on weight, platelet count, and white blood cell count mainly because of baseline differences between the groups, although these were not significant. Since pain was scored after inspection of the score from the previous visit this measurement was dependent; hence, an unpaired t-test for the endpoint values was performed. This test was also used to evaluate radiograph score.

For ANOVA models the treatment factor was regarded as fixed whilst the time and patient factors were assumed to be random. For all tests inspection and analysis of the residuals was carried out for model evaluation.[18] The residuals for morning stiffness, grip strength, and C-reactive protein were non-normal. Since no suitable transformations were found, the ANOVA was performed on the ranks rather than on the values themselves, thus yielding a large sample p value.[17]

The principle of intention to treat has been followed throughout this trial.[12] For drop-outs unrelated to treatment we extrapolated the last observed value, and for treatment-related drop-outs we used minimum value extrapolation. p values below 0·05 were regarded as significant.

Results

34 patients completed the trial, and table II lists the reasons for drop-outs. During the study period, 5 patients in the diet group reduced and 1 increased the consumption of NSAIDs; in the control group 3 patients reduced their consumption of these drugs.

After 1 month at the health farm patients showed decreases in the number of tender joints ($p < 0.0002$), in Ritchie's articular index ($p < 0.0004$), in the number of swollen joints ($p < 0.04$), in pain ($p < 0.0001$), in duration of morning stiffness ($p < 0.0002$), and in ESR ($p < 0.002$), C-reactive protein ($p < 0.005$), white blood cell count ($p < 0.0001$), and platelet count ($p < 0.006$). In the same period they had an increase in grip strength ($p < 0.0005$) and score on health assessment questionnaire ($p < 0.0001$). These gains were maintained throughout the year (figs 1 and 2).

The patients in the control group showed a decrease in pain score after their stay in the convalescent home ($p < 0.02$), but none of the other indices improved significantly, and at the end of the study they had deteriorated.

When the two groups were compared by t-test after 13 months, repeated measures ANOVA, and ANACOVA, a statistically significant improvement was seen in the diet group for all indices except platelet count and haemoglobin (figs 1 and 2). Both groups deteriorated slightly with respect to radiograph score, and in this respect they did not differ at the end of the trial.

The diet group lost more weight than the control group and showed a bigger drop in haemoglobin (though the latter was not significant). Albumin did not change significantly in either group. During the period on vegan diet the patients had difficulty in meeting some of their essential nutritional needs despite advice from the dietitian. However, when the diet was switched to lactovegetarian these problems were

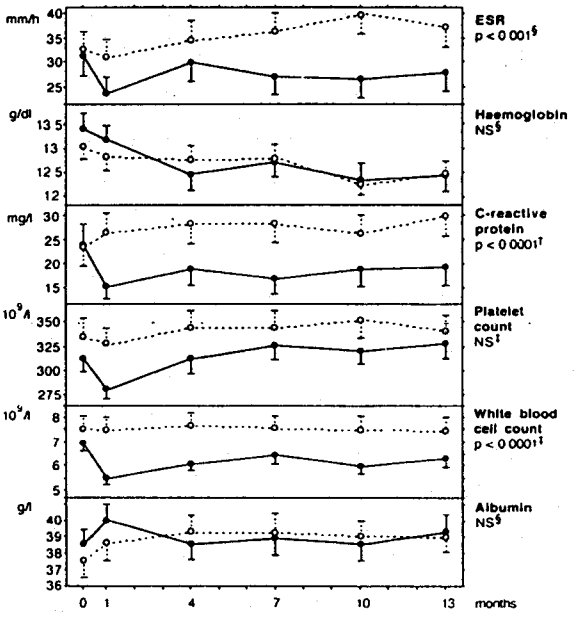

Fig 2—Laboratory values.

Mean and standard error of the mean for the diet group: ——●——. Mean and standard error of the mean for the control group: - - - -○- - - -. The p values refer to overall group differences. †Repeated measures ANOVA on the ranks. ‡ANACOVA. §Repeated measures ANOVA. NS = not significant.

eliminated (Haugen M, Kjeldsen-Kragh J, Skakkeback N, et al, unpublished).

When the statistical calculations were done only for patients who completed the study (drop-outs excluded), the principal conclusions remained the same (data not shown).

Discussion

Although most patients with rheumatoid arthritis benefit from a short period of fasting,[4,8,9] nearly all relapse on reintroduction of food. We have now shown that the improvement can be sustained by an individually adjusted dietary regimen. These results corroborate the findings of Darlington et al[6] and Beri et al[7] who likewise used an individually adjusted diet. In those two trials, however, the study period was only 3 months.

Since it is impossible to carry out double-blind trials of diet treatment, we had to choose a single-blind design. Participants had to be willing to be randomised to either group; however, most of them hoped to be randomised to the diet group, so we must consider the possibility of a negative placebo ("nocebo") effect in the control group as well as a placebo effect in the diet group. We think that such effects are unlikely to account for all the improvement seen in the diet group. If it was only a matter of placebo/nocebo effect, one would expect the difference between the two groups to diminish with time and to be negligible after 13 months. Furthermore, one would expect the gains to be mainly in the subjective and semi-objective indices rather than in ESR, C-reactive protein, white blood cell count, and number of swollen joints.

That an individually adjusted diet reduces disease activity suggests that food allergy or intolerance is involved to some degree in the pathogenesis of rheumatoid arthritis. About half of the patients in the present study reported some kind of allergy or intolerance. In a questionnaire based survey[19] we found that one-third of patients with rheumatoid arthritis had experienced aggravation of arthritis symptoms after intake of certain food items. In a double-blind food challenge study, Panush[3] reported deterioration in 3 of 15 patients with rheumatoid arthritis who claimed to have food allergy/intolerance and he estimated that such a condition might be found in 5% of patients with rheumatoid arthritis. It is difficult for the patient to recognise ill-effects from items that are consumed every day, so the proportion of patients with food allergy/intolerance might be higher than Panush suggests. In the present study, food allergy/intolerance was suspected in 10 (37%) of the 27 patients in the diet group. Food allergy/intolerance, however, is unlikely to explain the improvement in all the patients who changed their diet. Interest has been drawn to dietary fatty acids and their ability to modulate the inflammatory process.[20] A switch to vegetarian diet causes an extensive change of the profile of the fatty acids of the serum phospholipids.[21] These changes may favour production of prostaglandins and leukotrienes with less inflammatory activity.

We know that malnutrition suppresses immunity[22] and that treatment with immunosuppressive drugs is one of the most efficient means of reducing disease activity in rheumatoid arthritis. The diet group lost more weight than the control group, though albumin concentrations showed no difference. To evaluate whether the improvement was solely due to the weight reduction, an ANACOVA was done with weight reduction as a covariate. All p values were approximately the same as we obtained with the ordinary repeated measures ANOVA. Therefore, the weight reduction could explain only a small part of the improvement, and the overall conclusion remained the same.

Because of the nature of the study, in which participants had to be receptive to extensive changes in the diet, we cannot be sure that these patients are typical of those with rheumatoid arthritis. Nevertheless we have shown that in some patients a substantial reduction in disease activity can be obtained by fasting followed by an individually adjusted vegetarian diet. Despite the difficulties of covering essential nutritional needs during the first 4 months we do not believe that this regimen carries a health risk. On the contrary, it seems to be a useful supplement to the ordinary medical treatment.

We acknowledge financial support from the Norwegian Women's Public Health Association, the Anders Jahre's Fund for Promotion of Science, Isberg's Legacy, Grethe Harbitz Legacy, Eckbo's Legacy, and Nycomed Pharma AS, Oslo. We also thank the Department of Clinical Chemistry, National Hospital, Oslo, and the laboratories at the Red Cross Clinic, Oslo, and the Oslo Sanitetsforenings Rheumatism Hospital for analysis of the blood samples, and Gunnhild Wik Mikkelsen for her assistance in the study.

REFERENCES

1. Parke AL, Hughes GRV. Rheumatoid arthritis and food: a case study. *Br Med J* 1981; 282: 2027–29.
2. Panush RS, Stroud RM, Webster EM. Food-induced (allergic) arthritis. Inflammatory arthritis exacerbated by milk. *Arthritis Rheum* 1986; 29: 220–26.
3. Panush RS. Food induced ("allergic") arthritis: clinical and serologic studies. *J Rheumatol* 1990; 17: 291–94.
4. Sköldstam L, Larsson L, Lindström FD. Effects of fasting and lactovegetarian diet on rheumatoid arthritis. *Scand J Rheumatol* 1979; 8: 249–55.
5. Panush RS, Carter RL, Katz P, Kowsari B, Longley S, Finnie S. Diet therapy for rheumatoid arthritis. *Arthritis Rheum* 1983; 26: 462–71.
6. Darlington LG, Ramsey NW, Mansfield JR. Placebo-controlled, blind study of dietary manipulation therapy in rheumatoid arthritis. *Lancet* 1986; i: 236–38.
7. Beri D, Malaviya AN, Shandilya R, Singh RR. Effect of dietary restrictions on disease activity in rheumatoid arthritis. *Ann Rheum Dis* 1988; 47: 69–72.
8. Uden A, Trang L, Venizelos N, Palmblad J. Neutrophil functions and clinical performance after total fasting in patients with rheumatoid arthritis. *Ann Rheum Dis* 1983; 42: 45–51.
9. Hafström I, Ringertz B, Gyllenhammer H, Palmblad J, Harms-Ringdahl M. Effects of fasting in disease activity, neutrophil function, fatty acid composition, and leukotriene biosynthesis in patients with rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 585–92.
10. Ropes MW, Bennett GA, Cobb S, Jacox R, Jessar RA. 1958 revision of diagnostic criteria for rheumatoid arthritis. *Bull Rheum Dis* 1958; 9: 175–76.
11. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. *JAMA* 1949; 140: 659–62.
12. Pocock SJ. Clinical trials. A practical approach. New York: Wiley, 1984.
13. Fries JF, Spitz P, Kraines RG, Holman HR. Measurement of patient outcome in arthritis. 1980; 23: 137—45.
14. Ritchie DM, Boyle JA, McInnes JM, et al. Clinical studies with an articular index for the assessment of joint tenderness in patients with rheumatoid arthritis. *Q J Med* 1968; 37: 393–406.
15. Larsen A, Dale K, Eek M. Radiographic evaluation of rheumatoid arthritis and related conditions by standard reference films. *Acta Radiol Diag* 1977; 18: 481–91.
16. Statens Ernaeringsråd. Matvaretabell. (In Norwegian). Oslo: Landsforeningen for kosthold & helse, 1984.
17. Montgomery DC. Design and analysis of experiments. New York: Wiley, 1984: 117–31.
18. Kleinbaum DG, Kupper LL, Muller KE. Applied regression analysis and other multivariate methods. Boston: PWS-Kent, 1988: 96–314.
19. Haugen M, Kjeldsen-Kragh J, Nordvåg BY, Førre Ø. Diet and disease symptoms in rheumatic diseases—results of a questionnaire based survey. *Clin Rheumatol* (in press).
20. Kremer JM, Lawrence DA, Jubiz W, et al. Dietary fish oil and olive oil supplementation in patients with rheumatoid arthritis. Clinical and immunological effects. *Arthritis Rheum* 1990; 33: 810–20.
21. Phinney SD, Odin RS, Johnson SB, Holman RT. Reduced arachidonate in serum phospholipids and cholesteryl esters associated with vegetarian diets in humans. *Am J Clin Nutr* 1990; 51: 385–95.
22. Good RA. Nutrition and immunity. *J Clin Immunol* 1981; 1: 3–11.