

# Fasting followed by vegetarian diet in patients with rheumatoid arthritis: a systematic review

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Clinical experience suggests that fasting followed by vegetarian diet may help patients with rheumatoid arthritis (RA). We reviewed the available scientific evidence, because patients frequently ask for dietary advice, and exclusive pharmacological treatment of RA is often not satisfying. Fasting studies in RA were searched in MEDLINE and by checking references in relevant reports. The results of the controlled studies which reported follow-up data for at least three months after fasting were quantitatively pooled. Thirty-one reports of fasting studies in patients with RA were found. Only four controlled studies investigated the effects of fasting and subsequent diets for at least three months. The pooling of these studies showed a statistically and clinically significant beneficial long-term effect. Thus, available evidence suggests that fasting followed by vegetarian diets might be useful in the treatment of RA. More randomised long-term studies are needed to confirm this view by methodologically convincing data.

Key words: rheumatoid arthritis, fasting, diet, systematic review, meta-analysis

For a long time clinical observations have suggested that diets may improve RA (1–8). Nevertheless, until recently probably most rheumatologists would have denied a role for diet in the treatment of RA. Patients who have RA – in contrast – frequently feel improvement or worsening of symptoms with certain food components. Because most doctors do not encourage patients in their dietary efforts, often persons without medical qualifications advise patients with RA about their diet.

The scientific basis for a role of diet in RA has grown in the last years. After identification of eicosanoids, formed from arachidonic acids, as mediators in inflammation, the idea is supported that diet might influence RA: Vegetarian diet – as opposed to foods of animal origin – provides no arachidonic acid, reduces thus formation of eicosanoids, and has, therefore, presumably a beneficial impact on inflammatory diseases (9). It must be mentioned, however, that linolic acid which is also a precursor for pro-inflammatory eicosanoids is abundant in vegetarian diets. Dietary supplementation with  $\omega$ -3 fatty acids is meanwhile widely accepted as adjunctive therapy in RA (10). For a long time it has been hypothesised that the gut is importantly involved in the pathogenesis of RA. It would be beyond the scope of this paper to discuss all the physiological findings that contribute details to this general assumption. Two recent randomised studies,

however, must be mentioned, because they show rather directly and convincingly that a) fasting and vegan diet change the intestinal flora significantly and b) that change of intestinal flora correlates positively with treatment success (11, 12). Moreover, new findings suggest an important role for leptin in linking fasting and immunosuppression (13). Thus, there are not only several clinical findings that support the idea that fasting and diet influence RA positively, but there is also evidence for plausible physiological mechanisms that might cause such positive changes.

Fasting cures in RA have a long tradition (3–7), whereby fasting is usually applied within an holistic therapeutical approach which combines fasting under close supervision of a physician with exercise, physiotherapy, psychotherapy, and an educational programme. There is hardly any doubt that fasting has an anti-inflammatory effect and relieves pain during the period of fasting (14–18). After the termination of fasting, however, inflammation and symptoms usually flare up again within a few days. This means that fasting without further diet therapy seems to be of limited therapeutical value. Less clear is the evidence, whether there is a long term efficacy of fasting in RA when it is combined with a subsequent vegetarian diet. Kjeldsen-Kragh et al. (14) found significant long term effects of fasting with a subsequent vegetarian diet in a thoroughly conducted randomised study. The beneficial effects initially were shown for a period of 13 months and were still present after two years of diet (19). But other authors report less encouraging results (15, 16). To shed more light on the role of fasting in RA, a systematic review was carried out to identify all

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studies which report on fasting in RA, and the results of controlled trials were synthesized by a pooling of results.

## Materials and methods

### Inclusion criteria

Firstly, to get a comprehensive collection of empirical evidence all studies were included which investigated fasting in rheumatic diseases. At this step only case reports and animal studies were excluded for methodological reasons. In a second step all controlled clinical trials on fasting in RA which reported follow-up data for at least three months after treatment beginning were selected for statistical pooling of efficacy-findings. The time criterion of three months was chosen, because there is hardly any doubt that fasting ameliorates inflammation and pain in the short term and it is the long term efficacy that is at debate. Of course, a more prolonged evaluation period, e.g. twelve months, and a restriction to randomised trials only would have been desirable from a purely methodological point of view. But there is – with one exception (14) – no study that would meet these more demanding criteria. Therefore, to summarise the state of the art, it seemed necessary to include methodologically sub-optimal studies.

### Identification of trials

The database MEDLINE (1966–1997) was searched for entries in which fasting and rheumatic diseases were mentioned simultaneously, applying the following search strategy: “(rheum\* or arthri\* or collageno\* or polyarthr\* or ancylosan\* or (lupus and erythematod\*) or (panarth\* and nodos\*) or dermatomy\* or polymyo\* or spondyl\* or osteochond\*) and (fasting or fasted or fast or starv\*)”. Potentially relevant papers were identified, and their reference lists were checked for further studies. In addition experts in the field were approached.

### Data

From the different improvement criteria which were reported in most studies, we selected for the quantitative pooling the most sensitive indicator of each study according to Gøtsche (20). He had carried out a meta-analysis of 130 placebo controlled RCTs in RA to find the most sensitive indicators of improvement in drug therapy of RA. Because his results are clearly independent from the investigation reported here, this approach seemed appropriate to solve the otherwise awkward problem of selecting or

combining study parameters. In most of the studies which we analysed, the selected improvement criterion was a visual analogue scale of pain.

### Analyses and statistics

For pooled results an effect size *d* and its standard deviation was computed for each study. These *d*-values correspond to a standardised difference between treatment and control group in units of their pooled standard deviation. Because designs applied and statistics reported were different between the studies included, formulas given by Rosenthal (21) and by Shadish and Haddock (22) were used to estimate *d*-values. These *d*-values and their 95%-confidence-intervals are thought to describe the observations of different studies on a common scale. Pooling was conducted by combination of the *p*-values given in each publication, to avoid inaccuracies implied by the above transformations. As usual in meta-analysis of *p*-values one-sided values were calculated to ensure that significant results with different direction that actually contradict each other cancel out in the analysis.

## Results

Our approach detected 31 original reports on studies in which fasting was applied in patients with RA (Table I). Numerous physiological and clinical parameters were reported in detail and even psychological characteristics of patients who are willing to fast were empirically investigated in one study (23). Note that Table I contents only original articles, i.e. reviews and other articles which report and comment on fasting and RA are not listed. Also not listed is a thesis (24) which gives a rather topical overview on empirical findings to dietary treatment of RA. However the synthesis of these different results is unfortunately not straightforward. So the available evidence is open for different interpretations and there is no complete and widely accepted understanding of the mechanisms of fasting and diets in RA up to now.

One reason for this deficit is, that although many reports exist, in fact only a few independent studies and working groups investigated fasting in RA. Thus, only four independent controlled studies evaluated the clinical consequences of fasting followed by vegetarian diet for at least three months (Table II). All other references in Table I report only short term effects of fasting or relate to the same studies. Because these four controlled studies are crucial for a methodologically adequate clinical evaluation of fasting in RA which does not rely

on physiological speculations, these studies are presented here in some detail.

The most convincing evidence for long term efficacy of fasting followed by vegetarian diet comes from a study by Kjeldsen-Kragh et al. (14). Fifty-three patients with RA were randomly assigned to fasting or a control group. The assessment of efficacy was single-blind: the doctors who rated the patients did not know whether the patients had fasted or not. This randomised single-blind design is the methodological optimum for fasting studies, because, of course, patients can not be kept blind to the fact that they fast. The patients of the experimental group fasted for 7 up to 10 days and then took an individually adjusted vegan diet for 3.5 months. The basic vegan diet consisted of the same vegetables that were used in the form of juice or broth during the fast (potatoes, carrots, celery, parsley and beets). Additionally, every other day new food items were added which stayed in the diet when they did not worsen symptoms within 2 days. When a food item provoked symptoms repeatedly it was omitted from the diet. After 3.5 months patients were allowed to add milk, other dairy products and gluten-containing foods to this individually adjusted vegan diet. Thereafter, again new food items were introduced one at a time and were omitted when they were followed repeatedly by symptom worsening. After 13 months of this dietary regimen all clinical parameters and half of the laboratory parameters were significantly improved in the fasting group compared to the control group. Because this study seems to be the most important of the studies detected, some further methodological comments seem appropriate. As is typical for long-term studies and especially studies on more or less rigorous diets, there was a high drop out rate in this study also: only 34 patients (64%) completed the trial, whereby drop outs were approximately as frequent in the treatment group as in the control group. Statistically, the authors accounted for this problem by following the principle of intention to treat, and they note that analyses of complete cases only lead to the same principal findings. A further problem of this study is the possibility of a negative placebo (“nocebo”) effect in the control group: Obviously most of the participants of the study had hoped to be randomised to the treatment group and so the patients randomised to the control group may have shown worse results because of disappointment. This is a principal problem with randomised studies of this kind, i.e. when patients cannot be kept blind to the treatment. Kjeldsen-Kragh et al. argue with some plausibility that such effects should diminish with time and would be expected to be negligible after 13 months. Moreover, the observed differences in ESR,

C-reactive protein, white blood cell count, and number of swollen joints are difficult to explain by such a nocebo effect. Numerous further details of this study were reported in several additional articles (11, 19, 23, 40–45).

A further randomised and often cited study was done by Sköldstam et al. (15). Sixteen patients with RA fasted 7 up to 10 days followed by a 9 weeks lacto-vegetarian diet. Although the sum of these periods is somewhat less than our inclusion criterion of three months, in fact the follow-up data were assessed in the 12th week of the study and this period seemed sufficiently large to include the study. Otherwise we would have excluded one of two randomised studies only because of a seemingly negligible difference. The 10 patients of the control group consumed an omnivorous diet. Whereas the usual improvement during fasting was observed, there was no significant difference between fasting and control group after completion of the lacto-vegetarian diet. Neither drug usage nor clinical or biochemical variables differed significantly. Although the relatively small N and the unevenly distributed cases warrant caution in the interpretation of these non-significant results, it may be concluded that at least no strong effects of fasting and diet seemed to be present in this study. Possible reasons for the apparent discrepancy to the results of Kjeldsen-Kragh et al. (14) are stated in the discussion.

Sköldstam (16) investigated 20 patients with RA and assessed initially baseline data partially for two months and partially for five months. After baseline the patients fasted for seven to ten days and then followed a strict vegan diet. After a four weeks stay at a health farm the patients continued the vegan diet for a further three months at home. At the end of the trial patients felt significantly less pain compared to the baseline data and their functional capacity was significantly improved ( $p < 0.05$ ). Some objective parameters like erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), however, showed no significant improvement and Sköldstam concludes that fasting followed by a vegan diet improves subjective symptoms of patients with RA, but does not relevantly influence the disease itself.

Lindberg (25) fasted 12 patients with RA for 14 up to 23 days and subsequently gave a diet rich in bases. Thirty-two patients not willing to fast served as controls. The study was neither randomised nor blinded, and so selection effects and judgement biases are probable. According to current methodological standards the study must be regarded as insufficient in several respects. Lindberg reports a “highly significant” difference in improvement rates of the two groups ( $p < 0.0001$ ) and improvement

Table 1. Articles directly referring to studies on fasting in RA (in chronological order).

Authors	Year	Study design	Patients N(EG/CG)	Fasting		Following diet	Main results
				Duration	Kind		
Pirlet & Schlepfer (5)	1968	Observational study	30 RA	"short"	Tea and rusk	"change in diet"	Recommendation of therapy; more success with shorter duration of disease and longer duration of therapy.
Lindberg (25)	1973	Controlled study	44 RA (12/32)	14–23 days	Liquids	13 months diet rich in bases	9 of 12 patients completed dietary study; 6 were improved. In the control group only 1 patient was improved.
Lindahl & Myrnersts(26)	1978	Observational study	34 RA	1–3 weeks	?	12 months vegetarian	Joint index, activity index, and motion of fingers and hands significantly improved. Problems with compliance: only 18 patients followed the diet strictly for 12 months.
Sköldstam et al. (15)	1979	Randomised study	26 RA (16/10)	7–10 days	Tea and juice	9 weeks lacto-vegetarian	After fasting significantly less pain, stiffness, use of analgetics, clinical symptoms and serum concentrations of orosomucoid. After lacto-vegetarian diet no significant differences.
Trang et al. (18)	1980	Cross-over study	12 female RA	7 days	Total	None	With fasting continuous reduction of clinical parameters, inflammation and cAMP. High cAMP concentrations before fasting were correlated with clinical improvement.
Trang et al. (27)	1980	Cross-over study	12 female RA	7 days	Total	None	Before fasting the ratio cAMP/cGMP in urine was 10 to 1 (normal). In fasting the ratio cAMP/cGMP in urine on fasting days 2–4 which showed the maximum clinical response was significantly enlarged; in fasting cAMP was decreased in plasma and urine.
Wallentin & Sköldstam (28)	1980	Randomised study	12 RA (7/5)	10 days	Tea and juice	None	During fasting concentrations of lipid and lipoprotein and rate of cholesterol esterification significantly reduced.
Sundqvist et al. (29)	1982	Randomised study	10 RA (5/5)	10 days	Fruit and vegetable juice	10 weeks lacto-vegetarian	During fasting intestinal and non-intestinal permeability significantly reduced, during lacto-vegetarian diet again increased. Concomitantly a clinical six joint-score first decreased and then increased again.
Lithell et al. (30)	1983	Observational study	27 stationary patients	14 days	modified	3 weeks vegan	After fasting blood glucose and serum insulin concentrations were significantly lower than before the fast (p < 0.01). At the end of the diet the insulin/glucose ratio was lower than at the start of the fast. Serum enzyme concentrations reflecting liver function were increased during the fast.
Lithell et al. (31)	1983	Observational study	20 pat. with arthritis and different skin disorders	14 days	Modified	3 weeks vegan	During fasting, arthralgia less intense in many patients and improvement in some types of skin diseases. During the vegan diet symptoms returned in most patients.
Sköldstam et al. (32)	1983	Controlled study	18 RA (10/8)	10 days	Fruit juice	None	Controls showed depressed quantitative lymphocyte proliferation (LP) at the end of the fast (p < 0.05), but no change in concavalin-A-induced suppressor cell activity (conA-SC). Patients with RA showed subnormal LP and conA-SC before fasting (p < 0.05); after fasting they were clinically improved and LP and conA-SC had become normal.

Sköldstam et al. (33)	1983 Controlled study	14 RA/7 healthy controls	10 days	Fruit and vegetable juice	None	During fasting patients with RA and healthy controls showed reduced levels of complement factor 3(C3), orosomucoid and haptoglobin; reduction in C3 and orosomucoid more expressed in patients with RA than in healthy controls. Plasma albumin, IgG, IgA, IgM and complement factor 4 were not changed.
Trang et al. (34)	1983 Cross-over study	12 female RA	7 days	Total	None	Clinical and laboratory indices of inflammation were significantly reduced during fasting. cAMP and cGMP were subnormal in the control period but not the ratio cAMP/cGMP. During fasting the ratio cAMP/cGMP increased and was correlated with clinical improvement.
Uden et al. (35)	1983 Cross-over study	13 RA	7 days	Total	None	During fasting joint inflammation and ESR were reduced. During fasting locomotion of neutrophils under agarose, induced by a reference serum, decreased significantly ( $p < 0.001$ ), but no change in their locomotion was induced by an Escherichia coli bacterial factor. The bactericidal capacity improved during fasting significantly ( $p < 0.01$ ) and was associated with clinical improvement.
Wing et al. (36)	1983 Observational study	15 obese subjects	14 days	80 calories	None	Blood monocyte bactericidal activity and natural killer cell cytolytic activity were increased by fasting as were serum concentrations of IgG, IgA and IgM. Peripheral blood leukocyte counts did not decrease significantly.
Kroger et al. (17)	1984 Multicenter observational study	43 RA	4-9 days	Total	None	All 7 measured parameters of rheumatic activity were significantly improved compared to baseline ( $p < 0.001$ ), negligible side effects only
Trang et al. (37)	1985 Controlled study	12 female RA/8 healthy controls	7 days	?	None	RA was not characterised by a typical amino acid pattern. During fasting taurine showed an increase in patients with RA not observed in healthy volunteers and valine exhibited a smaller increment than that apparent in healthy controls.
Sköldstam (16)	1986 Controlled study	22 RA	7-10 days	?	4 months vegan	At the end of the diet there was a significantly reduced pain score but no significant differences in ESR, CRP, C3, grip strength, joint count and an index of joint tenderness
Hafström et al. (38)	1988 Cross-over study	14 RA	7 days	Total	None	"Disease activity decreased, as did the neutrophil release of lysozyme induced by the ionophore A23187. The ability of zymosan-activated RA patient serum to aggregate control neutrophils was reduced, together with serum concentrations of C3. The relative contents of arachidonic acid and eicosapentaenoic acid were increased in serum, platelets, acid and neutrophils, whereas levels of linoleic acid and linolenic acid were unchanged. Fasting also reduced the release of leukotriene B4 from neutrophils" (p. 585)
Korf et al. (39)	1989 Observational study	14 pat. with osteochondritis	?	Total	None	During fasting there was a strong decrease in linoleic and eicosatrienoic acids and an increase in palmitic, oleic and arachidonic acids in blood plasma.
Kjeldsen-Kragh et al. (14)	1991 Randomised study	53 RA (27/26)	7-10 days	Subtotal	Individually adjusted <sup>#</sup>	When the diet and the control group were compared after 13 months, a statistically significant improvement was seen in the diet group for all indices except platelet count, haemoglobin and radiograph score.



Table 1. Articles directly referring to studies on fasting in RA (in chronological order).

Authors	Year	Study design	Patients N(EG/CG)	Fasting		Following diet	Main results
				Duration	Kind		
Haugen et al. (40)	1993	Randomised study	34 RA(17/17)	7–10 days	Subtotal	Individually adjusted <sup>#</sup>	BMI and triceps skinfold thickness compared to baseline and compared to controls significantly reduced; insulin-like growth factor significantly reduced after 1 month compared to baseline.
Haugen et al. (11)	1994	Observational study	27 RA	7–10 days		Individually adjusted <sup>#</sup>	Concentrations of omega-6 fatty acids significantly reduced after vegan diet, but not reduced after lacto-vegetarian diet. Concentrations of omega-3 fatty acids were significantly reduced after both diets. No differences were found between diet responders and non-responders. Changes in the fatty acid profiles could not explain the clinical improvement observed.
Kjeldsen-Kragh et al. (19)	1994	Controlled study	45 RA (22/23)	7–10 days	Subtotal	Individually adjusted <sup>#</sup> ; then patients decided them self on their diet for further 12 months	The following parameters favoured diet responders: pain, duration of morning stiffness, SHAQ, number of tender joints Ritchie's index, number of swollen joints, ESR, platelet count and white blood cell count. Significant differences between groups for all clinical variables, except for grip strength. No significant differences with regard to laboratory or anthropometric variables.
Kjeldsen-Kragh et al. (23)	1994	Controlled study	53 RA in study vs. 71 other RA	7–10 days	Subtotal	Individually adjusted <sup>#</sup>	Participants of study showed significantly higher scores for internality, less confidence in conventional therapy and more confidence in alternative therapies
Peltonen et al. (41)	1994	Randomised study	53 RA (27/26)	7–10 days	Subtotal	Individually adjusted <sup>#</sup>	Omnivorous vs. vegan vs. lacto-vegetarian diet induced significant differences of the intestinal flora. The intestinal flora of diet responders and non-responders differed significantly.
Kjeldsen-Kragh et al. (42)	1995	Randomised study	53 RA (27/26)	7–10 days	Subtotal	Individually adjusted <sup>#</sup>	In diet group significant reduction of the number of thrombocytes and leukocytes, of total IgG, C3 activation products and complement components C3 and C4; no significant changes in control group; the number of leukocytes changed independently of clinical parameters.
Kjeldsen-Kragh et al. (43)	1995	Controlled study	27 RA vs. 30 healthy controls	7–10 days	Subtotal	Individually adjusted <sup>#</sup>	Elevated IgG and IgA antibody activity against alpha-lactalbumin in a significantly larger number of RA patients than in controls. With the exception of one patient, there was no concordance between the clinical course and antibody activity.

Study	Study Design	Patients	Duration	Subtotal	Individually adjusted <sup>#</sup>	Notes
Kjeldsen-Kragh et al. (44)	1995 Randomised study	53 RA (27/26)	7-10 days	Subtotal	Individually adjusted <sup>#</sup>	In diet group significantly reduced mean anti-proteus titres at all time points of the study, compared with baseline (p < 0.05). In control group no significant changes. Responders showed the highest reduction of anti-proteus titre. Total IgG concentration and levels of antibody against Escherichia coli were almost unchanged in all groups. The reduction in proteus antibody levels correlated significantly with the decrease in a modified Stoke disease activity index (p < 0.001).
Kjeldsen-Kragh et al. (45)	1996 Observational study	26 RA	7-10 days	Subtotal	3, 5 months individually adjusted vegan	The decrease in the proportion of agalactosyl IgG correlated significantly with the clinical improvement after fasting, but not after the vegan diet.
Trollmo et al. (46)	1997 Controlled study	7 RA, 17 healthy controls	3-6 days	Total	None	Fasting induced an enhanced antigen specific mucosa derived B lymphocyte response in patients with RA and in healthy volunteers. In contrast, the systemic B cell responses were not significantly changed.

EG: experimental group. CG: control group. #: elimination diet, 3.5 months vegan and 9 months lacto-vegetarian based. BMI= body mass index. SHAO= Stanford Health Assessment Questionnaire.

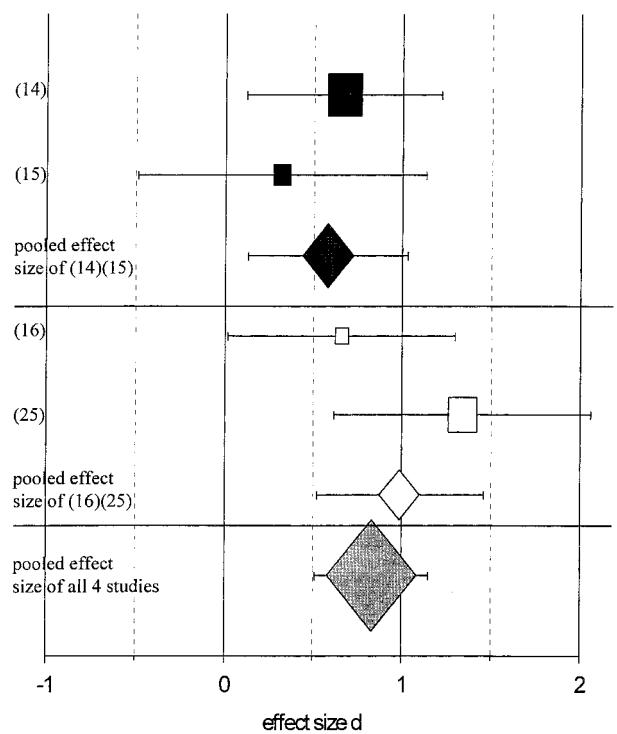


Fig. 1. Effect sizes d and their 95% confidence intervals for the four controlled studies on clinical long term effects of fasting and for the results of three meta-analyses. Solid squares mark randomised controlled trials and open squares mark non-randomised controlled trials; symbol sizes correspond to the respective number of patients included into analysis.

rates of 50% in the fasting group and 4% in the control group (intent-to-treat approach; this corresponds to a effect size d of 1.34 after transformation of the observed correlation in a d-value according to Rosenthal (21)).

Pooling of the p-values reported in Table II showed a significant beneficial effect of fasting followed by vegetarian diet when the results of the four controlled studies were combined (Figure 1, p < 0.0001, r = 0.38 which corresponds to a d of 0.83). The observed effect size of d = 0.83 is certainly large enough to be not only statistically significant but also clinically relevant. The studies of Sköldstam (16) and of Lindberg (25), however, were not randomised both and contributed therefore – and for other reasons – methodologically less convincing data to the pooled results. We therefore combined the results of the randomised controlled studies (14, 15) separately and again observed a significant improvement with fasting followed by diet (p < 0.01, r = 0.28 which corresponds to a d of 0.58). Thus, even if we ignore the supportive results of Lindberg (25) and Sköldstam (16) for methodological reasons, the available evidence still shows a significant beneficial effect of fasting and vegetarian diet in patients with RA, although the observed

Table II. Controlled studies on long term efficacy of fasting followed by vegetarian diet in RA.

Authors	Randomised?	N (EG,CG)	Duration	Fasting/diet	Criterion	Effect size d	Significance*
Kjeldsen-Kragh et al. (14)	Yes	53 (27,26)	13 months	7–10 days of fasting followed by an individually adjusted diet: 3.5 months vegan, 9 months lacto-vegetarian	VAS pain	0.67	<0.01
Sköldstam et al. (15)	Yes	26 (16,10)	3 months	7–10 days of fasting followed by lacto-vegetarian diet	VAS pain	0.32	= 0.20
Sköldstam (16)	No	20 <sup>#</sup> (20,20)	4 months	7–10 days of fasting followed by vegan diet	VAS pain	0.66	<0.025
Lindberg (25)	No	44 (12,32)	13 months	14–23 days of fasting followed by diet rich in bases	Improvement rates	1.34	= 0.0001

EG= number of patients in the experimental group, CG= number of patients in the control group, VAS= visual analogue scale, \* one-sided test, #: intra-individual design.

effect size  $d=0.58$  is clearly lower than when the non-randomised studies were included.

## Discussion

Our quantitative synthesis and the literature review support the hypothesis that a short period of fasting followed by a vegetarian diet can cause clinically relevant long term improvement in patients with RA. This statement holds for a statistical analysis of all four existing controlled studies (14–16, 25) as for the two randomised studies alone. The single most convincing piece of evidence is the randomised single-blind study reported by Kjeldsen-Kragh et al. (14) and the related articles (11, 19, 23, 40–45). Although Sköldstam et al. (15) found no significant effects with fasting and a lacto-vegetarian diet, there is no strict contradiction to the findings of Kjeldsen-Kragh et al. Firstly this result might be due to a lack of statistical power, since Sköldstam et al. investigated only approximately half as many patients ( $N=26$ ) as Kjeldsen-Kragh et al. ( $N=53$ ) and their results also show a tendency towards improvement. Secondly, the lacto-vegetarian diet used by Sköldstam et al. may be less efficacious than the individually adjusted, partially vegan diet that Kjeldsen-Kragh et al. gave their RA patients. Although there are diets that have negative impact on nutritional status (48), medically supervised fasting, lacto-vegetarian diets, and the procedure applied by Kjeldsen-Kragh et al. seem rather safe (40).

However, some limitations of our results must be pointed out. Firstly and most importantly, the number of rigorous, methodologically adequate clinical studies is too small to allow any final conclusions. Two randomised controlled studies do

not suffice to prove the efficacy of a therapeutic approach even when the evidence is encouraging. Thus, there is an urgent need for methodologically sufficient clinical studies which evaluate long term effects of fasting and diet. Of course this means also that the estimates of our quantitative synthesis can not be very precise and it is only the general support in favour of our hypothesis that is important here. That there is a lack of methodologically convincing studies does not mean, of course, that the respective treatment is insufficient. Rather it shows a typical research deficit that is due to difficulties in the funding of studies investigating other than drug treatments (49). Secondly, there is a well known publication bias in medical journals: negative – i.e. not significant – results are less likely to be accepted as papers and therefore we may have missed especially studies with negative results. Consequently the reported literature may yield a too positive impression of the efficacy of fasting and subsequent diets. We tried to minimise this bias by hand search and contact with experts and are not aware of any further study with negative results, but of course we can not completely exclude this possibility. The third limitation is that the results reported can not be generalised to all patients with RA. All the patients included in the studies reported here were eager to fast and were compliant with a rather rigorous dietetic procedure. We do not know how many patients with RA would be compliant with such a demanding therapeutic procedure, nor what the precise characteristics of these patients are. Thus, the present evidence only suggests that fasting and vegetarian diet seem to help a subgroup of patients with RA, and it seems too early for a general evidence based recommendation of this treatment approach (50). This may be not completely what we



want, but in relation to the risks and limited success of conventional drug therapy it deserves at least further careful investigation.

## References

- Hare DC. A therapeutic trial of a raw vegetable diet in chronic rheumatic conditions. *Proc R Soc Med* 1936;30:1–10.
- Hare DC, Pillman-Williams EC. Vitamin-C output in diet treatment of rheumatoid arthritis. *Lancet* 1938;234:20–5.
- Buchinger O. *Das Heilfasten und seine Hilfsmethoden*. Stuttgart: Hippokrates Verlag, 1935.
- Eisenberg W. Zur Behandlung des primär chronischen Gelenkrheumatismus durch Fasten. *Hippokrates* 1956;26:688–92.
- Pirlet K, Schlepper P. Physikalisch-diätetische Behandlung der progressiven chronischen Polyarthrit. *Archiv für physikalische Therapie* 1968;20:487–91.
- Fahrner H. *Fasten als Therapie*. Stuttgart: Hippokrates Verlag, 1985.
- Lützner H. Ernährungstherapie bei entzündlichen-rheumatischen Erkrankungen. *Rheuma* 1988;8:276–81.
- Seignalet J. Les associations entre HLA et polyarthrite rhumatoïde II: une théorie sur la pathogénie de la polyarthrite rhumatoïde. *Rev Int Rheumatol* 1989;19:155–70.
- Adam O. Anti-inflammatory diet in rheumatic diseases. *Eur J Clin Nutr* 1995;49:703–17.
- Cleland LG, James MJ. Rheumatoid arthritis and the balance of dietary N-6 and N-3 essential fatty acids. *Br J Rheumatol* 1997;36:513–4.
- Haugen MA, Kjeldsen-Kragh J, Bjerve KS, Høstmark AT, Førre Ø. Changes in plasma phospholipid fatty acids and their relationship to disease activity in rheumatoid arthritis patients treated with a vegetarian diet. *Br J Nutr* 1994;72:555–66.
- Peltonen R, Nenonen M, Helve T, Hanninen O, Toivanen P, Eerola E. Faecal microbial flora and disease activity in rheumatoid arthritis during a vegan diet. *Br J Rheumatol* 1997;36:4–8.
- Lord GM, Matarese G, Howard JK, Baker RJ, Bloom SR, Lechler RI. Leptin modulates the T-cell immune response and reverses starvation-induced immunosuppression. *Nature* 1998;394:897–901.
- Kjeldsen-Kragh J, Haugen M, Borchgrevink CF, Laerum E, Eek M, Mowinkel P, et al. Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis. *Lancet* 1991;338:899–902.
- Sköldstam L, Larsson L, Lindström FD. Effect of fasting and lactovegetarian diet on rheumatoid arthritis. *Scand J Rheumatol* 1979;8:249–55.
- Sköldstam L. Fasting and vegan diet in rheumatoid arthritis. *Scand J Rheumatol* 1986;15:219–21.
- Kroker GF, Stroud RM, Marshall R, Bullock T, Carroll FM, Greenberg M, et al. Fasting rheumatoid arthritis: a multicenter study. *Clin Ecology* 1984;2:137–44.
- Trang LE, Lövgren O, Bendz R, Mjos O. The effect of fasting on plasma cyclic adenosine-3', 5'-monophosphate in rheumatoid arthritis. *Scand J Rheumatol* 1980;9:229–33.
- Kjeldsen-Kragh J, Haugen M, Borchgrevink CF, Førre Ø. Vegetarian diet for patients with rheumatoid arthritis—status: two years after introduction of the diet. *Clin Rheumatol* 1994;13:475–82.
- Götsche PC. Sensitivity of effect variables in rheumatoid arthritis: a meta-analysis of 130 placebo controlled NSAID trials. *J Clin Epidemiol* 1990;43:1313–8.
- Rosenthal R. Parametric measures of effect size. In: H Cooper, LV Hedges, eds. *The handbook of research synthesis*. New York: Russel Sage Foundation, 1994:231–44.
- Shadish WR, Haddock CK. Combining estimates of effect size. In: H Cooper, LV Hedges, eds. *The handbook of research synthesis*. New York: Russel Sage Foundation, 1994:261–81.
- Kjeldsen-Kragh J, Haugen M, Førre Ø, Laache H, Malt UF. Vegetarian diet for patients with rheumatoid arthritis: can the clinical effects be explained by the psychological characteristics of the patients? *Br J Rheumatol* 1994;33:569–75.
- Kjeldsen-Kragh J. *Dietary treatment of rheumatoid arthritis*. Oslo: Oslo Sanitetsforening Rheumatism Hospital; 1995 (Thesis).
- Lindberg E. Können Ernährungsfaktoren die chronische Polyarthrit beeinflussen? *Zeitschrift für Physiotherapie* 1973;25:119–29.
- Lindahl O, Myrner R. Treatment of rheumatoid arthritis with a dietary regimen. *Swed J Biol Med* 1979;2:11–5.
- Trang LE, Lövgren O, Horn R, Walaas O, Mjos O. Cyclic nucleotides in rheumatoid arthritis. *Agents Actions* 1980;10:566–9.
- Wallentin L, Sköldstam L. Lipoproteins and cholesterol esterification rate in plasma during a 10-day modified fast in man. *Am J Clin Nutr* 1980;33:1925–31.
- Sundqvist T, Lindström F, Magnusson KE, Sköldstam L, Stjernström I, Tagesson C. Influence of fasting on intestinal permeability and disease activity in patients with rheumatoid arthritis. *Scand J Rheumatol* 1982;11:33–8.
- Lithell H, Vessby B, Hellsing K, Ljunghall K, Hoglund NJ, Werner I, et al. Changes in metabolism during a fasting period and a subsequent vegetarian diet with particular reference to glucose metabolism. *Ups J Med Sci* 1983;88:109–19.
- Lithell H, Bruce Å, Gustafsson IB, Höglund NJ, Karlström B, Ljunghall K, et al. A fasting and vegetarian diet treatment trial on chronic inflammatory disorders. *Acta Derm Venereol* 1983;63:397–403.
- Sköldstam L, Jorfelt L, Lindell B, Martensson J. Specific plasma proteins as indices of inflammation during a modified fast in patients with rheumatoid arthritis. *Scand J Rheumatol* 1983;12:161–5.
- Sköldstam L, Lindström FD, Lindblom B. Impaired conA suppressor cell activity in patients with rheumatoid arthritis shows normalization during fasting. *Scand J Rheumatol* 1983;12:369–73.
- Trang LE, Lövgren O, Norlund AE, Horn R, Walaas O. Cyclic nucleotides and catecholamines in rheumatoid arthritis. *Scand J Rheumatol* 1983;12:171–6.
- Uden AM, 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.
- Wing EJ, Stanko RT, Winkelstein A, Adibi SA. Fasting-enhanced immune effector mechanisms in obese subjects. *Am J Med* 1983;75:91–6.
- Trang LE, Furst P, Odeback AC, Lövgren O. Plasma amino acids in rheumatoid arthritis. *Scand J Rheumatol* 1985;14:393–402.
- Hafström I, Ringertz B, Gyllenhammar H, Palmblad J, Harms-Ringdahl M. Effects of fasting on disease activity, neutrophil function, fatty acid composition, and leukotriene biosynthesis in patients with rheumatoid arthritis. *Arthritis Rheum* 1988;31:585–92.
- Korf II, Tsagikian TA, Meshcheriakova VA, Levachev MM, Arutiunova MB. Izmenenie sostava zhirnykh kislot plazmy krovi i eritrotsitov pri osteokhondroze. *Vopr Med Khim* 1989;35:81–4.

40. Haugen MA, Kjeldsen-Kragh J, Skakkebæk N, Landaas S, Sjaastad O, Movinkel P, et al. The influence of fast and vegetarian diet on parameters of nutritional status in patients with rheumatoid arthritis. *Clin Rheumatol* 1993;12:62–9.
41. Peltonen R, Kjeldsen-Kragh J, Haugen M, Tuominen J, Toivanen P, Førre Ø, et al. Changes of faecal flora in rheumatoid arthritis during fasting and one-year vegetarian diet. *Br J Rheumatol* 1994;33:638–43.
42. Kjeldsen-Kragh J, Mellbye OJ, Haugen M, Mollnes TE, Hammer HB, Sioud M, et al. Changes in laboratory variables in rheumatoid arthritis patients during a trial of fasting and one-year vegetarian diet. *Scand J Rheumatol* 1995;24:85–93.
43. Kjeldsen-Kragh J, Hvatum M, Haugen M, Førre Ø, Scott H. Antibodies against dietary antigens in rheumatoid arthritis patients treated with fasting and a one-year vegetarian diet. *Clin Exp Rheumatol* 1995;13:167–72.
44. Kjeldsen-Kragh J, Rashid T, Dybwad A, Sioud M, Haugen M, Førre Ø, et al. Decrease in anti-Proteus mirabilis but not anti-Escherichia coli antibody levels in rheumatoid arthritis patients treated with fasting and a one year vegetarian diet. *Ann Rheum Dis* 1995;54:221–4.
45. Kjeldsen-Kragh J, Sumar N, Bodman-Smith K, Brostoff J. Changes in glycosylation of IgG during fasting in patients with rheumatoid arthritis. *Br J Rheumatol* 1996;35:117–9.
46. Trollmo C, Verdrengh M, Tarkowski A. Fasting enhances mucosal antigen specific B cell responses in rheumatoid arthritis. *Ann Rheum Dis* 1997;56:130–4.
47. Kjeldsen-Kragh J, Kvaavik E, Bottolfs M, Lingaas E. Inhibition of growth of Proteus mirabilis and Escherichia coli in urine in response to fasting and vegetarian diet. *APMIS* 1995;103:818–22.
48. Wolman PG. Management of patients using unproven regimens for arthritis. *J Am Diet Assoc* 1987;87:1211–4.
49. Dieppe P, Chard J, Tallon D, Egger M. Funding clinical research. *Lancet* 1999;353:1626.
50. Mangge H, Hermann J, Schauenstein K. Diet and rheumatoid arthritis – a review. *Scand J Rheumatol* 1999;28:201–9.