

**WEIGHT REDUCTION IS NOT A MAJOR REASON FOR IMPROVEMENT IN RHEUMATOID
ARTHRITIS FROM LACTO-VEGETARIAN, VEGAN OR MEDITERRANEAN DIETS.**

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ABSTRACT

Objectives

Several investigators have reported that clinical improvements of patients with rheumatoid arthritis (RA) from participating in therapeutic diet intervention studies have been accompanied by loss of body weight. This has raised the question whether energy undernutrition per se can improve RA. In order to test this hypothesis, three previously conducted diet intervention studies, comprising 102 patients with RA, were pooled. The five effect variables were defined as the difference (Δ) from baseline to conclusion of the study calculated for ESR, acute phase response, pain-score, physical function, and tender joint count. Reduction in body weight (Δ body weight), type of diet (ordinary diet or test diet), age, gender, and disease duration were independent variables. Multiple logistic regression was used in order to analyse associations between the independent and the effect variables.

Results

Statistically significant correlations were found between diet and three effect variables i.e. acute-phase response, pain-score, and physical function. Body weight reduction was univariately only correlated to acute-phase response (but, accordingly, not significant when diet was taken into account).

Conclusions

Body weight reduction does not significantly contribute to the improvement in rheumatoid arthritis that some patients have from eating lacto-vegetarian, vegan or Mediterranean diets.

Key words

Rheumatoid Arthritis, therapy, diet intervention, lacto-vegetarian diet, vegan diet, Mediterranean diet, body weight.

INTRODUCTION

We have recently found that patients with rheumatoid arthritis (RA) improved significantly in disease activity from eating a modified Cretan Mediterranean diet (MD) for 12 weeks (1). Improvement was seen in 9 of 14 efficacy variables. The DAS28 (2) was improved by 13 %. In comparison the control group showed no change. The outcome of the study indicated that specific, so far not identified, factors from the MD were suppressive to the RA inflammation. However, at the end of the experiment the patients of the diet group but not the control group had lost 3 kg in weight ($p < 0.001$ between groups), although our ambition had been to prescribe a MD that was isocaloric compared to the patients' previous food intake. This unexpected weight loss raised the question whether a reduced energy intake, could explain the clinical improvement.

Long-term pure energy under-nutrition without other mal-nutrition has anti-inflammatory effects in mice (3). In humans, deliberately undertaken short term fasting is well known to induce immune suppression and improvement in RA disease activity (4). There are no controlled long-term studies of reduction of the energy intake without mal-nutrition on patients with RA. Iwasahige et al. (5) recently conducted a regimen for 54 days of caloric restriction combined with fasting in ten patients with RA. The patients lost in weight, and interestingly, the composite disease activity score of Lansbury was significantly reduced. In connection with diet intervention studies several investigators (6-11) have reported that their patients have lost in weight and with some studies (1,10) there have been a statistically significant correlation between clinical improvement and weight reduction.

We have until now conducted three diet intervention studies (1,6,7) on patients with RA. In each of these experiments, the patients had obtained a statistically significant weight loss on

the intervention diet. In order to enable a more trustworthy statistical analysis, data from these previous studies were pooled. Thus, with a larger number of cases, the aim of this present study was to investigate whether weight loss independently had contributed to the improvement.

METHODS

Design and patients

Data from three different diet intervention studies, which we had previously conducted on patients with rheumatoid arthritis, were pooled and reanalysed.

The first one, which was published in 1979 (6), was a prospective, randomised, parallel, open study over three months, on 26 patients of 35 - 66 years of age, with rheumatoid arthritis of 4 - 33 years of duration. 24 patients had concluded the trial. 14 had eaten the tested lacto-vegetarian diet, and 10 an ordinary western diet. At the end of the experiment the group of diet patients had lost 3.5 kg in body weight. Eight of them had reported a decrease in pain. As a group they had shown no statistically significant improvement in disease activity measurements.

The second study, which was published in 1986 (7), was a prospective, cross over, open study on 22 patients of 35 – 68 years of age, with rheumatoid arthritis of ½ - 30 years of duration. 13 patients had been followed for 2 months and 7 for 5 months on their ordinary diet. After this initial control period all patients had adopted a vegan diet for the next four months. 20 patients had concluded the trial. As a group the patients had lost 4.8 kg in weight during the vegan diet period. They had showed statistically significant reduction in pain score, and improvement in functional capacity. No change had occurred in painful joint counts, or in blood laboratory measurements.

The third study was from 2003 (1). It was a prospective, randomised, open study over three months on 56 patients of 33 – 75 years of age, with rheumatoid arthritis of 2 –59 years duration. 51 had concluded the trial. 26 had tested a Cretan Mediterranean diet. 25 had had

their own ordinary diet. At the end of the experiment, the group of diet patients had lost 3 kg in body weight. This group had shown improvement in 9 out of 14 efficacy variables.

Altogether our pooled patient material comprises 97 individuals with rheumatoid arthritis.

Due to the cross over design of the second study the number of cases are 102. Their demographic data are given in table 1. All except one had active disease. The pharmacological treatment as well as eventual dietary supplementation (e.g. fish oils, vitamins, minerals, etc.) had been kept constant from beforehand and throughout the experiment.

60 cases had been followed for 3 - 4 months on an experimental diet, i.e. 14 on a lacto-vegetarian diet for 3 months (1st study), 20 a vegan diet for four months (2nd study) and 26 a traditional Cretan diet for 3 months (3rd study).

35 cases had been followed as controls on their ordinary western diets for three months (1st and 3rd studies) and another 7 cases for 5 months (2nd study). Thirteen patients had been followed as controls for only two months (2nd study), and were therefore not included as controls in the present study.

Outcome variables

For evaluation of RA disease activity five different measures were comparable in all three studies. These measures were:

1. The Westergren erythrocyte sedimentation rate (ESR)
2. The acute-phase response (12), which had been measured as the serum concentration (s-) of orosomucoid in the first study and as s- C-reactive protein (CRP) in the two last studies.
3. Pain-score, which was the patient's self perceived pain severity as evaluated on a visual analogue scale (VAS, 0-100 mm).

4. Physical function, which were by the patient self completed questionnaires on the degree of difficulty in performing specified tasks of daily living. In the first study performed with a locally produced questionnaire, in the second, with a not yet validated Swedish version of the Stanford-health assessment questionnaire (HAQ), and in the third study with the official Swedish version of HAQ (13).
5. Tender joint count (2), which in the first study was measured with the Ritchie index (14) and in the other two with the number of tender joints from palpation of 40 (second study), respectively, of 28 peripheral joints (third study).

Data analysis and statistics

Effect/dependant variables: For evaluating the effect of the intervention on RA disease activity, the difference (Δ) from baseline to the end of each study, in each of the five variables above was calculated; Δ ESR, Δ acute phase response, Δ pain-score, Δ physical function, and Δ tender joint count. These differences (Δ) were then categorised as reduction/improvement, or as no reduction/no improvement.

Independent variables: Gender, age, disease duration, type of diet (ordinary or control diet vs. the intervention diet (Mediterranean, lacto-vegetarian, or vegan diets)), and body weight reduction were used as independent variables. Age were categorised in <56 yrs or ≥ 56 yrs and disease duration (<9.5 yrs or ≥ 9.5 yrs) as well as changes in body weight (reduction or no reduction).

Statistics: Baseline characteristics of the two diet groups were tested with non parametric tests (Mann-Whitney's U-test, Table 1). Logistic regression (univariate and multivariate) was used in order to analyse associations between the independent and the dependent variables. All independent variables considered potentially significant were initially included in the model

followed by a step-wise deletion of the least significant variable until a significant level of 0.05 or less. The statistical analyses were made using a commercially available computer programme (STATISTICA, StatSoft[®], Tulsa, USA) and a p-value less than 0.05 was considered statistically significant.

RESULTS

At baseline, no significant differences in age, gender, body weight and disease duration were found between the two groups (Table 1) nor in ESR (not shown). Comparable absolute baseline estimations of pain-score, acute phase response, physical function or tender joint count are not available due to their different definitions during the three intervention studies. Nevertheless, as explained in methods, changes of these variables during the study periods are well defined.

The three tested diet regimens all of them rendered the patients a weight fall of on the average 2,4 kg .

The only statistically significant correlations, using multiple logistic regression, were between diet and three of the five effect parameters (acute-phase response, pain-score and physical function, but not ESR or tender joint count (Table 2 and 3). Body weight reduction was univariately only correlated to acute-phase response (but, accordingly, not statistically significant when diet was taken into account).

DISCUSSION

The results of this study are very clear. The three tested diets i.e. lacto-vegetarian, vegan and traditional Cretan Mediterranean, all of them had rendered the patients a weight fall of on the average 2.4 kg over the trial length of 3-4 months. Apart from a univariate correlation between improvement in acute phase response and reduction in body weight, no statistically significant correlation was seen between weight loss and the concomitantly obtained change in RA disease measurements. Thus it seems unlikely that loss of weight was an important factor behind the anti-inflammatory effect that the patients had had from the lacto-vegetarian, vegan or Mediterranean diets.

The multiple logistic regression analysis, showed highly significant statistical correlations between diet intervention and improvement in the RA outcome variables. These data strongly indicate that dietary factors have a potential to reduce RA inflammation. With regards to vegan diet, our proposal is supported by the results of at least two independent, randomised and controlled studies (9, 15). The crucial beneficial factors that these different diets share need to be identified. Noteworthy candidates are their high content of fruits and vegetables, as well as their relatively low content of saturated fats. These circumstances are discussed more extensively elsewhere (1), as is the therapeutic efficacy of these diets.

Overweight reduction is a recommended strategy for lowering insulin resistance. Patients with active RA have a pathologic peripheral insulin resistance (16). Whether nutritional therapies aiming to reduce insulin resistance have any additional anti inflammatory effect is yet an open question. Ideally, potential regulatory effects that weight reduction may have on RA should be studied for itself with diets that differ only in their contents of energy. We know of two small studies on deliberately undertaken weight reduction in patients with RA. In an uncontrolled pilot study (17) with 19 overweight patients with RA, Danish researchers had instructed the patients to reduce their energy intake by 30% to achieve weight reduction. After

a period of 12 weeks, the mean weight loss was 4.5 kg. No change was obtained in joint pain, morning stiffness, number of tender joints, or in sedimentation rate. Neither did Gordon et al. from their uncontrolled pilot study report any short-term favourable effects from assisting obese RA patients to reduce their body weight (18).

Before conclusion of this discussion we need to remember that there is a controversy in letting patients with RA test an experimental regiment, which would involve prolonged reduction of their energy intake. According to Walsmith and Roubenoff (19) most RA patients including those with overweight will develop a muscle wasting condition known as rheumatoid cachexia. Although not directly fatal, this form of cachexia is believed to contribute to co-morbidity and reduced life expectancy. It is caused by the rheumatoid inflammation by itself and is refractory to nutritional therapy. The logic therapeutic approach would be dual (18), firstly to control the inflammatory process and secondly to advocate physical exercise programs.

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Table 1. Baseline characteristics of patients who completed the trials.

	Diet group (n=60)	Control group (n=42)
Age (years)	54.5 (33-73)	57.0 (35-75)
Gender (M/F)*	11/49	7/35
Weight (kg)	72.1 (40-109)	69.4 (41-102)
Disease duration (years)	13.0 (0.5-59)	11.9 (2-35)

Footnotes to table:

Data are presented as mean (range) unless otherwise stated.

* Number of male and females, respectively

Table 2.

Odds ratios (OR) and corresponding p-values in univariate logistic regressions. Bolded values are statistically significant.

OR	Independent variable														
	Gender			Age (yrs)			Diet			Duration (yrs)			ΔBody weight		
Effect variable	M	F	p	<56	≥56	p	Control	Case	p	<9.5	≥9.5	p	<0	≥0	p
ΔESR	1.00	1.02	0.98	1.00	1.22	0.62	1.00	1.29	0.55	1.00	1.00	1.00	1.00	1.64	0.29
Δacute-phase res	1.00	0.60	0.33	1.00	0.74	0.45	1.00	3.27	0.007	1.00	1.17	0.69	1.00	2.85	0.03
Δpain-score	1.00	0.47	0.18	1.00	0.65	0.29	1.00	3.43	0.004	1.00	1.27	0.55	1.00	2.10	0.10
ΔPhys. function	1.00	0.86	0.78	1.00	0.74	0.45	1.00	4.22	0.002	1.00	1.38	0.42	1.00	2.16	0.10
ΔTender joint c	1.00	0.93	0.90	1.00	1.54	0.28	1.00	1.54	0.29	1.00	1.22	0.62	1.00	1.77	0.20

Footnotes to table:

ESR = The Westergren erythrocyte sedimentation rate

The acute-phase response = s-orosomuroid or s-C-reactive protein (CRP)

Pain-score = the patient's self perceived pain severity as evaluated on a visual analogue scale

Physical function = self completed questionnaires on the degree of difficulty in performing specified tasks of daily living.

Tender joint count = number of painful joints at rest with pressure

Table 3.

Odds ratios (OR) and 95% confidence intervals (95% CI) for the only statistically significant independent variable, diet (control diet vs. intervention diet) when using multiple logistic regression analysis. The three effect or dependent variables were changes in acute-phase response (Δ acute-phase), patient perceived pain severity (Δ pain-score) and patient physical function (Δ physical). The other two studied effect variables, Δ ESR and Δ tender joint count, were not significantly associated with any of the independent variables and are, therefore, not shown.

	Control diet			Intervention diet				
	Imp/no imp	Imp (%)	OR	Imp/no imp	Imp (%)	OR	95% CI	p
Δ acute-phase res	12/30	29	1.00	34/26	57	3.27	1.39 – 7.67	0.007
Δ pain-score	17/25	40	1.00	42/18	70	3.43	7.93 – 1.49	0.005
Δ physical funct	10/31	24	1.00	34/25	58	4.22	10.28 - 1.73	0.002

Footnotes to table:

ESR = The Westergren erythrocyte sedimentation rate

The acute-phase response = s-orosomuroid or s-C-reactive protein (CRP)

Pain-score = the patient's self perceived pain severity as evaluated on a visual analogue scale

Physical function = self completed questionnaires on the degree of difficulty in performing specified tasks of daily living.

