EXTENDED REPORT

An experimental study of a Mediterranean diet intervention for patients with rheumatoid arthritis

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Objective: To investigate the efficacy of a Mediterranean diet (MD) versus an ordinary Western diet for suppression of disease activity in patients with rheumatoid arthritis (RA).
Methods: Patients with well controlled, although active RA of at least two years' duration, who were receiving stable pharmacological treatment, were invited to participate. All patients were randomly allocated to the MD or the control diet (CD). To achieve good compliance with prescribed diets all patients were for the first three weeks served the MD or the CD, respectively, for lunch and dinner at the outpatient clinic's canteen. Clinical examinations were performed at baseline, and again in the 3rd, 6th, and 12th week. A composite disease activity index (DAS28), a physical function index (Health Assessment Questionnaire (HAQ)), a health survey of quality of life (Short Form-36 (SF-36)), and the daily consumption of non-steroidal anti-inflammatory drugs were used as primary efficacy variables.
Results: From baseline to the end of the study the patients in the MD group (n=26) showed a decrease in DAS28 of 0.56 (p<0.001), in HAQ of 0.15 (p=0.020), and in two dimensions of the SF-36 Health Survey: an increase in "vitality" of 11.3 (p=0.018) and a decrease in "compared with one year earlier" of 0.6 (p=0.016). For the control patients (n=25) no significant change was seen at the end of the study. This difference between the two treatment groups was notable only in the second half of the trial.
Conclusion: The results indicate that patients with RA, by adjusting to a Mediterranean diet, did obtain a reduction in inflammatory activity, an increase in physical function, and improved vitality.

Case-control studies indicate that lifelong consumption of fish,[1] olive oil,[2 3] and cooked vegetables[3] may have independent protective effects on the development or severity of rheumatoid arthritis (RA). Epidemiological studies from selected geographical regions support these hypotheses. From the Faroe Islands where peoples' diet is high in fish and whale meat, RA was reported to take a mild form.[4] In north-western Greece where the consumption of olive oil is high, the prevalence of RA has been reported to be low.[5]

Besides investigating the effects of specific nutrients and food items, attention should also be drawn to the diet as a whole. Ever since the Seven Countries Study[6] the Mediterranean diet (MD), particularly the Cretan MD, has been regarded as a healthy and disease preventing diet.[7] The traditional Cretan MD is characterised by a high consumption of fruit, vegetables, cereals, and legumes.[8] Compared with common Western diets the MD contains less red meat and more fish. The Cretan MD typically uses olive oil as the primary source of fat, and also includes a moderate intake of wine.

It is intriguing for rheumatologists to note that this kind of MD, in secondary prevention of coronary heart disease, was reported to reduce the recurrence rate of new cardiac events.[9] The pathogenesis of atheromatosis involves inflammatory processes[10] with obvious similarities to those of rheumatoid synovitis. In the atherosclerotic plaque microenvironment, as in RA synovitis, macrophages are the principal, inflammatory mediators with the ability to form numerous growth factors and cytokines.

We present a single centre, randomised, parallel study over three months. As far as we know, it is the first formal investigation of the efficacy of a Cretan MD for suppression of disease activity in patients with RA.

PATIENTS AND METHODS

Patients

Patients were recruited from the population of 200 000 people of the province of Kalmar in southeastern Sweden. Within the area practically all newly diagnosed cases of RA are referred to one of two rheumatology centres for specialist consultation. From the patient registers, 300 suitable candidates for the study were identified and invited by letter; 100 answered. Owing to every day commitments to jobs, family, etc, many were forced to withdraw, and others because of the exclusion criteria. All patients were informed orally and in writing about the study design, the underlying hypothesis, and of the right for the participant to withdraw from the project at any time, and for whatever reason.

The inclusion criteria were (*a*) RA according to the 1987 American College of Rheumatology criteria; (*b*) a disease duration of at least two years; (*c*) clinically the disease must have been characterised as stable and under adequate control as assessed and documented by the patient's own rheumatology specialist at the latest consultation before the trial.

A number of exclusion criteria prevented patients from participating. The disease modifying antirheumatic drugs (DMARDs) had to be unchanged for ⩾3 months, corticosteroids for ⩾4 weeks, and non-steroidal anti-inflammatory drug (NSAID) for ⩾10 days before beginning. The daily dose of oral corticosteroids could not exceed 12.5 mg of prednisolone. At the baseline assessments the disease activity score from 28 joints (DAS28) had to be >2.0 indicating active disease.[11] Except for RA, the patients could have no other condition that demanded active medical attention. Patients who were vegetarians or who already lived on a Mediterranean-like diet were also excluded.

Abbreviations: BMI, body mass index; CD, control diet; CRP, C reactive protein; CVD, cardiovascular disease; DAS, disease activity score; DMARD, disease modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; GAT, grip ability test; HAQ, Health Assessment Questionnaire; MD, Mediterranean diet; NSAID, non-steroidal anti-inflammatory drug; ORP, outpatient based rehabilitation programme; RA, rheumatoid arthritis; SF-36, Short Form-36 Health Survey; SOFI, signals of functional impairment; VAS, visual analogue scale

Table 1 Baseline characteristics of patients who completed the trial. Data are presented as mean (range) unless otherwise stated

	Diet group (n=26)	Control group (n=25)
Age (years)	58 (33–73)	59 (35–75)
Sex (men/women)*	5/21	5/20
Body mass index (kg/m^2)	28.4 (21.5–38.7)†	25.6 (16.4–31.4)
Fasting blood glucose (mmol/l)	5.0 (4.4–5.9)	5.2 (4.1–6.4)
Disease duration (years)	17 (2–59)†	10 (2–30)
Rheumatoid factor positive*/ANF positive*	19/7	20/5
Erosive disease positive*	20	23
DAS28, score	4.4 (2.19–7.00)	4.3 (2.2–6.9)
Current drugs		
NSAID*/equivalent mg of diclofenac	21/56	21/62
Corticosteroids*/mg of prednisolone	12/3.5	10/5.0
DMARD*, mono-/combination therapy	18/6	16/4
Methothrexate‡	14/10.9	11/8.2
Sulfasalazine‡	4/2000	4/2000
Chloroquine‡	2/180	2/160
Cyclosporin‡	3/125	2/163
Auranofin‡	0	1/6
Leflunomide‡	0	1/20

*Number of patients; †statistically significant difference between diet group and control group, $p<0.05$. Differences between groups were analysed by Student's *t* test for independent samples, except for differences in number of patients, which were evaluated by Pearson χ^2 or Fisher's exact test; ‡number of patients/mean dose in mg.

Design

The study designed was a single centre, randomised, parallel study over three months.

Consecutively, from September 1998 to November 2000, groups of two to six of the specially recruited patients started on the outpatient based rehabilitation programme (ORP)* provided by the rheumatology unit at Kalmar hospital. On the second day, and after the completion of the baseline assessments, all study patients were randomly allocated to continue with regular food (control diet (CD) group), or to change over to the MD (MD group). The randomisation was stratified for sex and it was done by block randomisation, with two to six patients in each block. Throughout the three weeks of the ORP, lunch and dinner were served to the patients according to the randomisation result. For the remaining nine weeks after the ORP, all patients returned home and back to their everyday life. The CD patients continued with their ordinary diet. The MD patients were instructed to continue with the MD diet, which they had to prepare themselves.

The patients' daily doses of DMARD and corticosteroids remained constant throughout the experiment. The individual dose of NSAID could be adjusted, but as with all other clinical events this had to be recorded in the study protocol. Dietary supplementation—for example, vitamins, minerals, fish oil capsules, etc, that the patients, had taken before the study, was documented. All such supplementary prescriptions had to be kept unchanged throughout the experiment.

Diets

We wanted to test the Cretan MD of de Lorgeril, *et al*,[9] for patients with RA. Both olive oil and canola (rapeseed) oil were allowed for food preparation, baking, and in salad dressings. The patients were provided with a liquid margarine (80% fat) for cooking and a spreadable margarine (40% fat) to use on bread, both of which were based on canola oil.

To suit Swedish subjects we adjusted the MD in certain aspects. The Cretan diet contains only small amounts of diary products, predominantly yoghurt and cheese,[8] whereas Swedes in general consume higher amounts of milk, fermented milk, and other dairy products. To eliminate the difference in consumption of dairy fats, our MD patients were asked to reduce the amounts of these food items or to choose low fat dairy products.

No recommendations were given about alcohol consumption. To compensate for the polyphenols present in wine, we encouraged the MD group to drink green or black tea.

To promote good compliance, an MD from the hospital canteen was served to our MD patients for the first three weeks. During these weeks each group of MD patients had six lessons from a dietician about Mediterranean food and cooking. After the ORP the same dietician was available weekly for telephone consultation and every third week for consultation in her office.

All MD patients got written instructions and recipes to facilitate the preparation of meals at home. The meals that both the MD and the control patients had to prepare at home were (*a*) every day breakfast and evening snacks; (*b*) meals for two weekends during the ORP; (*c*) every meal for the remaining nine weeks that followed the ORP. To further enhance compliance, some food items were supplied free to the MD patients—namely, olive oil, canola oil, liquid margarine, spreadable margarine, frozen vegetables, and tea.

The control patients were served ordinary hospital food during the ORP. For the rest of the study they were asked not to experiment by themselves, but to return to their usual diets.

Compliance with experimental and control diets was ascertained by a questionnaire, and by dietary history interviews that were validated with biological markers of food intake. The questionnaire was designed to examine food choices and it was specifically aimed at investigating compliance with the MD. The results of the dietary assessments and analysis of biological markers will be presented elsewhere.

Clinical assessments

Clinical examinations were performed at baseline (1st and 2nd day), at the end of the ORP (3rd week), at the halfway point (6th week), and at the end of the study (12th week).

Four measures were chosen as primary efficacy variables.

1 DAS28 was used for clinical assessment of disease activity. It is a composite disease activity index and also a response index

*Outpatient based rehabilitation programme (ORP): For years the rheumatology unit at Kalmar Hospital has run a rehabilitation programme for outpatients. Every third week, groups of six patients are scheduled to start on the programme, which runs for three weeks and covers Monday to Friday from 0900 to 1700. The programme offers patient education, strength and fitness training, and individual physiotherapy and occupational therapy.

Table 2 Clinical indices of disease activity at baseline and weeks 3, 6, and 12. Data are presented as mean (SD)

	Diet group (n=26)				Control group (n=25)				
	week 1	week 3	week 6	week 12	week 1	week 3	week 6	week 12	p Value*
DAS28 score (2–10)	4.4 (1.2)		4.2 (1.4) p=0.145‡	3.9 (1.2) p<0.001	4.3 (1.4)†		4.2 (1.4)† p=0.623	4.3 (1.5)† p=0.694	0.047
HAQ score (0–3)	0.7 (0.5)		0.6 (0.5)§ 0.148	0.6 (0.4) p=0.020	0.8 (0.6)†		0.7 (0.6)† p=0.484	0.8 (0.6)† p=0.208	0.012
Swollen joint count (0–28)	7.0 (5.6)§		6.3 (5.7)§ p=0.135	5.2 (5.1)§ p<0.001	6.9 (5.0)¶		7.8 (5.7)¶ p=0.154	7.5 (5.7)¶ p=0.516	0.001
Tender joint count (0–28)	6.8 (5.9)§		5.1 (5.0)§ p=0.041	4.5 (5.1)§ p=0.002	6.9 (6.3)¶		5.9 (5.9)¶ p=0.139	6.1 (6.4)¶ p=0.277	0.212
ESR (Westergren) (mm/1st h)	24 (15)	28 (20) p=0.070	31 (23) p=0.027	25 (15) p=0.596	23 (15)	26 (20) p=0.190	22 (15) p=0.710	25 (19) p=0.360	0.660
Patients' global VAS (0–100 mm)	30 (22)	20 (16) p=0.005	26 (21) p=0.267	18 (13) p=0.008	28 (20)	19 (14) p=0.007	26 (21) p=0.627	27 (21) p=0.694	0.061
Pain VAS (0–100 mm)	32 (20)	22 (16) p=0.004	30 (22) p=0.769	20 (13) p=0.007	31 (20)	25 (18) p=0.091	33 (24) p=0.570	34 (21) p=0.319	0.006
Morning stiffness (min)	49 (42)	35 (33) p=0.003	49 (49) p=0.998	44 (52) p=0.514	64 (38)	53 (44) p=0.142	70 (51) p=0.391	70 (64) p=0.531	0.367
CRP (mg/l)	17 (20)§	16 (22)§ p=0.475	27 (55)¶ p=0.965	12 (15)§ p=0.001	15 (14)†	15 (16)† p=0.293	12 (9)† p=0.152	15 (12)† p=0.525	0.006
Thrombocyte count (×10⁹/l)	273 (55)	250 (59)¶ p=0.005	258 (51) p=0.020	247 (47) p=0.001	306 (69)	300 (58)¶ p=0.331	291 (59) p=0.040	299 (74) p=0.470	0.131
GAT score (0–276)	26 (13)		24 (14) p=0.153	23 (13) p=0.110	23 (8)		24 (10) p=0.290	24 (11) p=0.590	0.121
SOFI score (0–44)	10.2 (6.8)§		9.4 (6.2)§ p=0.420	9.7 (7.0)§ p=0.520	10.2 (5.8)		9.0 (6.2) p=0.067	9.0 (5.6) p=0.165	0.647

*The p values refer to difference between diet and control groups for the change from baseline to week 12. Differences between groups were analysed by Student's *t* test for independent samples, except for HAQ score, number of swollen and tender joints, CRP, and SOFI score, evaluated by Mann-Whitney U test; †n=23; ‡the p values refer to change from baseline. Within-group differences at weeks 3, 6, and 12 compared with baseline, were evaluated by Student's *t* test for paired samples, except for HAQ score, number of swollen and tender joints, CRP, and SOFI score, which were evaluated by Wilcoxon signed ranks test; §n=25; ¶n=24.

Table 3 Quality of life reported by the patients using the Swedish SF-36 Health Survey. Data are presented as mean (SD)

	Diet group (n=26)			Control group (n=25)		
	Baseline	Mean difference from baseline to week 12	p Value*	Baseline	Mean difference from baseline to week 12	p Value*
Physical function	58.9 (20.9)	+2.5 (15.2)	0.533	55.4 (20.7)	+1.4 (13.4)	0.524
Physical role	55.8 (44.3)	+16.3 (43.6)	0.072	63.0 (39.6)	–11.0 (38.2)	0.199
Bodily pain	58.7 (24.0)	+4.5 (24.3)	0.426	54.4 (18.7)	+4.0 (20.1)	0.199
General health	58.7 (19.0)	+5.7 (14.6)	0.073	53.8 (20.7)	+0.7 (21.7)	0.818
Vitality	59.6 (24.6)	+11.3 (20.7)	0.018	54.0 (19.0)	+4.2 (16.3)	0.274
Social functioning	83.7 (22.8)	+4.8 (19.0)	0.286	88.1 (15.1)	–5.4 (18.8)	0.289
Emotional role	79.5 (37.8)	+9.0 (39.5)	0.230	78.6 (31.9)	+1.4 (27.9)	0.776
Mental health	79.9 (21.4)	+6.5 (16.5)	0.050	74.7 (15.3)	+3.7 (12.9)	0.143
Compared with one year earlier	2.7 (0.7)	–0.6 (1.1)	0.016	2.9 (1.0)†	–0.1 (1.0)†	0.793

*p Values refer to change from baseline to week 12. Within-group differences were evaluated by Wilcoxon signed ranks test; †n=23.

with good discriminatory validity.[11] It includes the 28 joint counts for tenderness (tender joint count) and swelling (swollen joint count), the Westergren erythrocyte sedimentation rate (ESR), and the patient's global assessment of disease activity on a horizontal visual analogue scale (patient global VAS, 0–100 mm).

2 The second primary efficacy variable was the Swedish version of the Health Assessment Questionnaire (HAQ),[12] which the patients answered to assess physical function.

3 Thirdly, the Swedish version of the Short Form-36 Health Survey (SF-36) was used for the patients to report health related quality of life. The test measures multidimensional health concepts including levels of wellbeing.[13]

4 The fourth variable was the patient's daily dose of NSAID, which was calculated from the mean daily dose of the past week and transformed to the equivalent dose of diclofenac.

Another 10 measures were used as secondary efficacy variables. Firstly, the four components of the DAS28 score.[11]

Table 4 Body weight and concentration of plasma lipids at baseline and weeks 3, 6, and 12. Data are presented as mean (SD) unless otherwise stated

	Diet group (n=26)*				Control group (n=25)†				
	week 1	week 3	week 6	week 12	week 1	week 3	week 6	week 12	p Value‡
Body weight (kg)	78.9 (14.2)			75.9 (13.5)§	73.0 (12.8)			72.6 (13.0)	<0.001
Range	55.6–109.3			52.5–106.7	53.2–102.3			53.8–102.2	
Plasma cholesterol (mmol/l)	5.9 (1.1)	5.2 (1.2)§	5.4 (1.0)§	5.5 (1.2)¶	5.5 (1.0)	5.3 (1.0)	5.5 (1.0)	5.3 (1.0)	0.131
Plasma triglycerides (mmol/l)	1.6 (0.8)	1.3 (0.5)	1.4 (0.6)	1.3 (0.5)	1.2 (0.5)	1.2 (0.6)	1.3 (0.6)	1.1 (0.5)	0.179

*n=25 for body weight, plasma cholesterol at week 6, and plasma triglycerides at week 6 owing to missing data; †n=23 for body weight owing to missing data; ‡the p values refer to difference between diet and control groups for the change from baseline to week 12. Differences between groups were analysed by Student's *t* test for independent samples.
Significant change from baseline: §p<0.001; ¶p<0.01. Within-group differences at weeks 3, 6, and 12 compared with baseline were evaluated by Student's *t* test for paired samples.

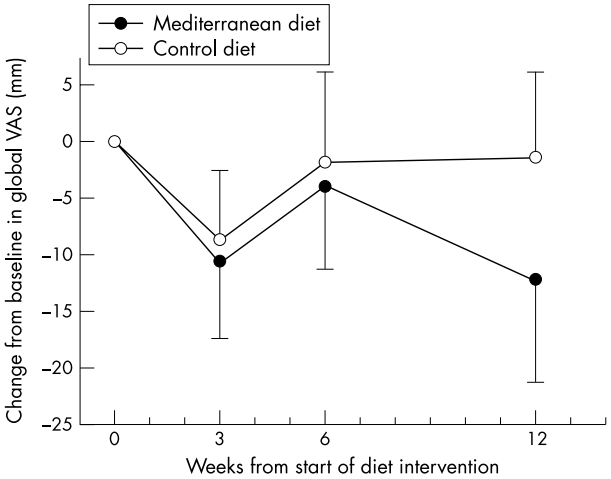

Figure 1 Patient's global assessment of disease activity by means of a VAS (0–100 mm) at baseline and weeks 3, 6, and 12. The results are presented in relative terms, where the baseline value is set to zero, as mean values with 95% confidence intervals.

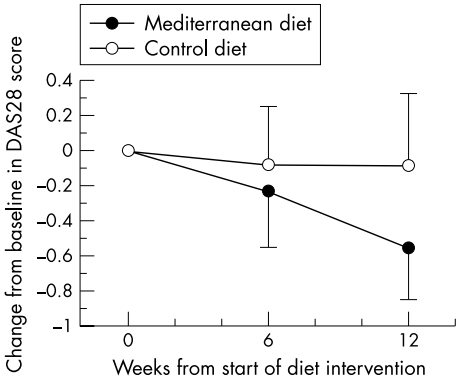

Figure 2 Disease activity (DAS28 score) at baseline and at weeks 6 and 12. The results are presented in relative terms, where the baseline value is set to zero, as mean values with 95% confidence intervals.

The serum concentration of C reactive protein (CRP)[14] and the peripheral venous blood thrombocyte count (thrombocyte count) were used as measures of the acute phase. The patients evaluated their own pain severity on a VAS (pain VAS, 0–100 mm) and their latent period before resolution of early morning stiffness (morning stiffness, minutes). The signals of functional impairment (SOFI) test is a quickly performed index of arm and leg functions, which was originally developed for patients with early RA.[15] The grip ability test (GAT) is a quick measure of hand function and its response to treatment.[16]

Nurse LM instructed the patients on how to use the two different VAS scales, how to report morning stiffness, and how to answer the HAQ and the SF-36 questionnaires. The SOFI test was assessed by a physiotherapist, and the GAT by an occupational therapist. The assessments of tender and swollen joints counts were performed by one specially trained nurse. Except for LM these officials had no other responsibility related to the project. No special directions were given to ensure that they were unaware of the study protocol.

Statistical methods

Statistical analyses were done using SPSS for Windows version 10.0. Differences between groups were evaluated by the Mann-Whitney U test for discrete variables, and Student's *t* test for independent samples was used for continuous variables. However, for differences in CRP, owing to skew distribution, the Mann-Whitney U test was performed. Differences in qualitative variables were analysed by Pearson χ^2 or Fisher's exact test.

Within-group differences at weeks 3, 6, and 12 when compared with baseline, were evaluated by Wilcoxon signed ranks test for discrete variables and CRP, while Student's *t* test for paired samples was performed for continuous variables.

RESULTS

A total of 56 patients were enrolled, of whom 29 were randomly allocated to the MD and 27 to the CD. Five patients were excluded from the final evaluation. Two of them were control patients, who at the baseline assessment, had an inactive disease with a DAS28 of <2.0. The other three belonged to the MD group. Firstly, one man left the trial after 10 days because of a lack of motivation. Another man had, after two weeks, a relapse of a rheumatoid pleuritis and was forced to raise his dose of prednisolone. Thirdly, after three weeks, a woman had to abandon the MD owing to dyspepsia.

Four violations to the protocol in the form of intra-articular injections with triamcinolone hexacetonide were reported. An MD patient had a knee joint injected in his second week. Two control patients had an elbow injected in their first and third week, respectively. A third control patient had a wrist and two finger joints injected in her sixth week and also began a two week long course of oral steroids. None of these patients were excluded. The joint counts were assessed independently of given injections. Hence, 26 diet and 25 control patients completed the study.

At the start of the trial the two treatment groups were equal in all respects except for disease duration and body mass index (BMI; table 1). The disease duration of the MD patients was 17 years compared with 10 for the controls (p=0.047). The mean BMI differed with 28.4 kg/m^2 for the MD group compared with

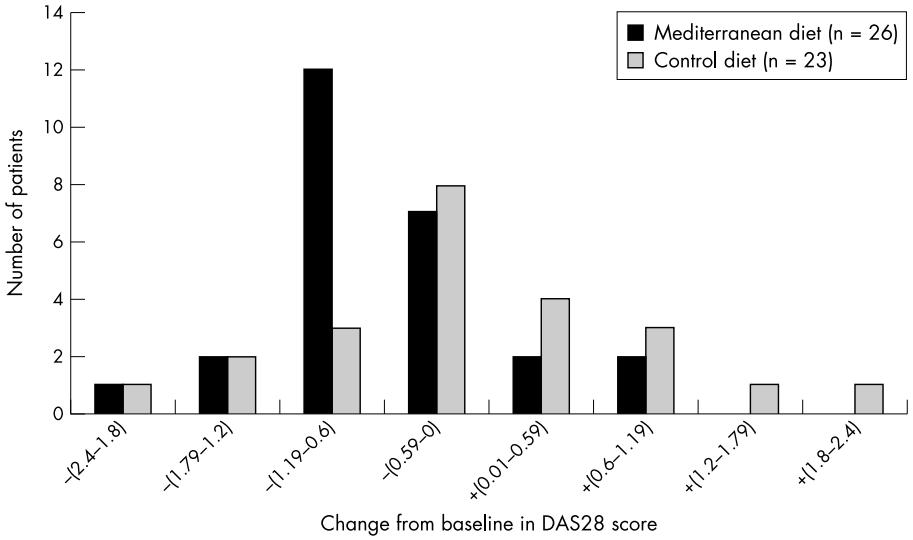

Figure 3 Distributions of change in DAS28 score. A change in DAS28 score >0.6 is considered to be a change of clinical significance.

a lower value of 25.6 kg/m^2 (p=0.024) for the controls. Seven diet and four control patients were obese with a BMI ⩾30 kg/m^2.

The two groups had equal smoking habits. At the start of he trial both groups had five every day smokers. Occasional smokers were two in the MD group and three in the CD group.

Thirty nine patients had a DAS28 of >3.2, indicating moderate or high disease activity. Four diet patients and eight in the control group were in the range of low disease activity with a DAS28 of between 2.0 and 3.2.

Table 2 summarises both the baseline values and the changes of all efficacy variables that took place during the trial period. At baseline no difference was seen between the MD and the control groups.

At the end of the ORP (3rd week), secondary efficacy variables for the patients of both groups had improved. Both the diet group and the control group reported a decrease in the patient global VAS (fig 1). The MD group also showed a reduction in the pain VAS, morning stiffness, and in thrombocyte counts. At that time the results for the two groups did not differ.

After six weeks, the patient global VAS was back to the baseline levels (fig 1). Both groups showed some isolated and diverging changes from the baseline values (table 2). At the end of the study (12th week), three of four primary variables of efficacy had improved in comparison with the baseline assessments for the patients in the MD group. Firstly, the DAS28 was reduced, with a drop of 0.56 (p<0.001). This reduction essentially occurred from the 6th to the 12th week (fig 2). Secondly, the HAQ had decreased by 0.15 (p=0.020). Thirdly, the SF-36 Health Survey had improved in two dimensions (table 3). Only the NSAID use was unaffected.

The outcome in the secondary efficacy variables in the 12th week was favourable to the MD group, which showed improvement in six of the 10 variables (table 2). The control group, on the other hand, showed no change in any efficacy variable after 12 weeks.

In summary, at the end of the trial nine of 14 efficacy variables had improved in the MD group, whereas the control group showed no changes at all.

Individually, 15 patients of the MD group had shown "moderate" or better clinical improvement with a decrease of >0.6 in the DAS28, as compared with six for the control patients (p=0.026) (fig 3). Only two MD patients, versus five for the controls, had shown worsening, with an increase in DAS28 of >0.6.

For the MD group, DAS28 (p=0.047), HAQ (p=0.012), swollen joint count (p=0.001), CRP (p=0.006), and pain VAS (p=0.006) had improved at the end of the study compared with baseline.

During the trial, the patients in the MD group lost 3.0 kg in weight (p<0.001), while the control patients maintained their weight (table 4). There was no correlation between the difference in DAS28 (from baseline to week 12) and weight loss.

Compared with baseline, the patients of the MD group showed a decrease in plasma cholesterol after only three weeks (p<0.001) and continued to stay below baseline in the 6th (p<0.001) and 12th weeks (p=0.008) (table 4). The control group showed no change.

Smoking habits did not change during the trial.

DISCUSSION

The main aim of the study was to test if the Cretan Mediterranean diet had a suppressive effect on rheumatoid inflammation. A study of the therapeutic value of an MD had of course to wait until the efficacy of the MD had been proved. A complete therapeutic evaluation will require larger numbers of patients to be followed up for a longer time, another budget, and collaboration with other centres.

When designing the study we made some assumptions. Firstly, we assumed that any effect of the MD was likely to follow a similar time course to that of fish oils. It has been shown that supplementation of an ordinary Western diet with fish oils induces a weak anti-inflammatory effect.[17] In patients with RA this effect was not detectable until after six weeks.[18] Our second assumption was that the efficacy of our MD would be modest at best. Thus, it was of utmost importance to achieve optimal compliance of the patients and to have as few drop outs as possible. Therefore we decided to choose a relatively short length of diet intervention.

The local ORP service was deliberately exploited as an important component of the study design to promote optimal patient compliance with their MD and CD, respectively. By this arrangement we could serve the patients the MD for three weeks. Several other methods were used to encourage compliance. From previous diet trials we were impressed with how well the patients with RA seemed to have complied with the prescribed diets,[19 20] and this study left us with the same impression. Important indicators were the fall in body weight and in serum cholesterol of the MD group.

For the inclusion criteria it may seem remarkable that some patients from the start had a DAS28 of up to 7.0. However, "stable and under adequate control" was the clinical judgment of the patients own doctor at the most recent visit of the

patient before the start of the study. Many patients had longstanding disease, and had tried all kinds of DMARD, including combination therapies. Under such circumstances the clinician and his patient may have come to a consensus that "there was adequate control". Of course, with a newly diagnosed disease this would have been unacceptable.

Few patients dropped out. Dyspepsia in one patient was the only reported side effect from the MD. One patient had a reoccurrence of rheumatoid pleuritis, which was considered unrelated to the diet regimen.

Supplementary treatment is often needed during the course of clinical studies on RA. If patients receiving such treatment are excluded, this may result in substantial loss of patient data. To some extent this problem can be reduced by guidelines in the study protocol, which should regulate the use of so called "rescue medication". In our study, four patients were given intra-articular injections with triamcinolone hexacetonide as supplementary treatment. Obviously, these were violations of the study protocol. However, one belonged to the MD group and three were control patients. Except for one of the controls, the injections were given early in the course of the trial. We considered that these supplementary treatments would have had only an insignificant effect on the study result. If they had affected the study results this would not have been in favour of the results of the MD.

Volunteers in a dietary intervention study will of course see what food they buy, prepare, and eat. In practice, it is therefore impossible to use a double blind design when comparing the effects on health of an MD and an ordinary northern European diet. Others have practised a single blinded approach by letting uninformed outsiders do the clinical assessments. Our assessors were familiar with the study protocol and were not forbidden to speak to the participating patients. Obviously our study design would not entirely control for effects of placebo and nocebo.[18] Recently, the concept of a powerful placebo effect, in general, has been questioned.[21] In our previous studies of diet in patients with longstanding RA, placebo and nocebo effects were of little significance.[19 20] With regards to the question of placebo it is interesting to examine the patients global VAS results (fig 1). For the first half of the study, the global VAS results of the two treatment groups followed each other very closely. At the end of the initiating ORP most patients of both groups reported an improved wellbeing. Half way through the trial these improvements were mostly lost, indicating that there was not yet any significant effect of the MD. Only after three months of diet intervention was the efficacy of the MD detectable and statistically significant.

We know of no other dietary intervention study on patients with RA which has tested the MD. de Lorgeril and coworkers studied a Cretan MD for secondary prevention of cardiac vascular disease, and reported that the diet reduced the recurrence of new events.[9] However, the Danish diet intervention study by Hansen *et al*,[22] in patients with RA is of certain interest. It was based on a scientific concept which is related to ours, and links intermediary metabolism with immunity and chronic inflammation. Hansen and coworkers tested a diet, which contained reduced amounts of fat, an increase in protein, especially of fish, and had a high content of antioxidants. Their dietary intervention lasted for six months, but was confounded by some problems with compliance. However, their results were still consistent with ours. The patients who were receiving the special diet showed significant improvements in morning stiffness, the number of swollen joints, and in their pain score. Interestingly, Hansen, *et al*, also saw a correlation between the decrease in body weight and the reduction in swollen joint numbers.

There are so far no formal studies on the long term efficacy of an MD in patients with RA. Our study was three months long, but it is our intention to present a one year follow up study. In theory even a minor effect that is persistent and accumulates over time might become important. The three studies from Greece indicate that long term consumption of an MD is beneficial.[2 3 5] If so, living on a lifelong MD might improve long term physical function, quality of life, and other disease outcome measurements.

At the start of the trial although randomly allocated to a diet, our two patient groups were not equal in all aspects. The first difference, disease duration, is unlikely to have had any bearing on the outcome results. The second difference, a higher BMI in MD patients than in controls, deserves attention. Firstly, BMI was high for both groups. In fact seven diet patients and four controls were, by definition, obese (BMI >30 kg/m^2). Data from Roubenoff *et al* indicate that patients with RA tend to have a cytokine driven cellular cachexia.[23] However, this does not mean that patients with RA in general are underweight. On the contrary, in a cohort of 79 ordinary American patients with RA, 40% had varying degrees of obesity.[24] At least three previous studies[25] have found an increased risk of developing RA in those who are significantly overweight. Symmons *et al* recently reported that a BMI of >30 kg/m^2 in a cohort of women was associated with an adjusted odds ratio of 3.74 (95% confidence interval 1.14 to 12.27) for developing RA.[25] Clinical reports say that patients with RA are at an increased risk of developing cardiovascular disease (CVD),[26] and, interestingly, obesity is a recognised risk factor for CVD,[10] and possibly for RA.[25] Weight loss has commonly been reported in response to dietary intervention for patients with RA.[19 20 22 27 28] However, unlike Hansen *et al*,[22] other researchers have seen no correlation between the patient's decrease in body weight and the positive clinical results obtained. We intend to examine BMI and other possible mechanisms of action more extensively in a forthcoming report, when our results for dietary assessments and analyses of biological markers are complete.

The fish consumed in Greece contain fewer n–3 fatty acids than deep ocean fish. This may explain why Linos and coworkers in their Greek case-control study found no significant evidence that fish consumption was an independent predictor of risk for RA.[3] Instead, the two independent predictive factors turned out to be consumption of olive oil and cooked vegetables. Olive oil is rich in oleic acid (18:1n–9), which can be metabolised to eicosatrienoic acid (20:3n–9) with anti-inflammatory effects similar to those of n–3 PUFA from fish oils.[3] Olive oil also has antioxidative properties. Greeks mainly consume the unrefined and unbleached virgin oil, which is rich in natural antioxidants including tocopherols.[3]

The other independent predictor of risk was consumption of cooked vegetables. Vegetables are particularly rich in a variety of natural antioxidants, which contribute to better control of inflammation. Antioxidants limit pathological aspects of the cytokine mediated response to inflammation. They also inhibit direct damage to tissues from all kinds of oxidative molecules that are released.[17]

In conclusion, the results of this intervention study indicate that a Cretan Mediterranean diet suppresses disease activity in patients who have stable and modestly active RA. Thus, by eating an MD for three months patients with RA can obtain better physical function and increase their vitality.

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REFERENCES

1 **Shapiro JA**, Koepsell T, Voight LF, Dugowson CE, Kestin M, Nelson JL. Diet and rheumatoid arthritis in women: a possible protective effect of fish consumption. Epidemiology 1996;7:256–63.
2 **Linos A**, Kaklamanis E, Kontomerkos A, Koumantaki Y, Gazi S, Vaiopoulos G, *et al*. The effect of olive oil and fish consumption on rheumatoid arthritis: a case control study. Scand J Rheumatol 1991;20:419–26.
3 **Linos A**, Kaklamani VG, Kaklamani E, Koumantaki Y, Giziaki E, Papazoglou S, *et al*. Dietary factors in relation to rheumatoid arthritis: a role for olive oil and cooked vegetables? Am J Clin Nutr 1999;70:1077–82.
4 **Recht L**, Helin P, Rasmussen JO, Jacobsen J, Lithman T, Scherstén B. Hand handicap and rheumatoid arthritis in a fish-eating society (the Faroe Islands). J Intern Med 1990;227:49–55.
5 **Drosos AA**, Alamanos I, Voulgari PV, Psychos DN, Katsaraki A, Papadopoulos I, *et al*. Epidemiology of adult rheumatoid arthritis in northwest Greece 1987–1995. J Rheumatol 1997;24:2129–33.
6 **Keys A**. *Seven countries: a multivariate analysis of death and coronary heart disease*. Cambridge and London: Harvard University Press, 1980.
7 **Trichopoulou A**, Vasilopoulou E. Mediterranean diet and longevity. Br J Nutr 2000;84(suppl 2):205–9.
8 **Kromhout D**, Keys A, Aravanis C, Buzina R, Fidanza F, Giampaoli S, *et al*. Food consumption patterns in the 1960s in seven countries. Am J Clin Nutr 1989;49:889–94.
9 **de Lorgeril M**, Renaud S, Mamelle N, Salen P, Martin J-L, Monjaud I, *et al*. Mediterranean alpha-linolenic acid rich diet in secondary prevention of coronary heart disease. Lancet 1994;343:1454–9.
10 **Ross R**. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993;362:801–9.
11 **van Riel PLCM**, van Gestel AM. Clinical outcome measures in rheumatoid arthritis. Ann Rheum Dis 2000;59(suppl I):i28–31.
12 **Ekdahl C**, Eberhardt K, Andersson SI, Svensson B. Assessing disability in patients with rheumatoid arthritis: use of a Swedish version of the Stanford-Health Assessment Questionnaire. Scand J Rheumatol 1988;17:263–71.
13 **Sullivan M**, Karlsson J, Ware JE Jr. The Swedish SF-36 health survey: 1. Evaluation of data quality, scaling assumptions, reliability and construct validity across general populations in Sweden. Soc Sci Med 1995;41:1349–58.
14 **Emery P**, Luqmani R. The validity of surrogate markers in rheumatic disease. Br J Rheumatol 1993;32(suppl 3):3–8.
15 **Eberhardt K**, Svensson B, Moritz U. Functional assessment of early rheumatoid arthritis. Br J Rheumatol 1988;27:364–71.
16 **Dellhag B**, Bjelle A. A grip ability test for use in rheumatology practice. J Rheumatol 1995;22:1559–65.
17 **Grimble RF**. Nutritional modulation of cytokine biology. Nutrition 1998;14:634–40.
18 **Sköldstam L**. Diets. In: Firestein GS, Panayi GS, Wollheim FA, eds. *Rheumatoid arthritis: new frontiers in pathogenesis and treatment*. Oxford: Oxford University Press, 2000:407–8.
19 **Sköldstam L**, Larsson L, Lindström FD. Effects of fasting and lactovegetarian diet on rheumatoid arthritis. Scand J Rheumatol 1979;8:249–55.
20 **Sköldstam L**. Fasting and vegan diet in rheumatoid arthritis. Scand J Rheumatol 1986;15:219–23.
21 **Kaptchuk TJ**. Powerful placebo: the dark side of randomized controlled trial. Lancet 1998;351:1722–5.
22 **Hansen GVO**, Nielsen L, Kluger E, Thysen M, Emmertsen H, Stengaard-Pedersen K, *et al*. Nutritional status of Danish rheumatoid arthritis patients and effects of diet adjustment in energy intake, fish-meal, and antioxidants. Scand J Rheumatol 1996;25:325–30.
23 **Roubenoff R**, Roubenoff RA, Cannon JG, Kehayias JJ, Zhuang H, Dawson-Hughes B, *et al*. Rheumatoid cachexia: cytokine-driven hypermetabolism accompanying reduced body cell mass in chronic inflammation. J Clin Invest 1994;94:2379–86.
24 **Morgan SL**, Andersson AM, Hood SM, Matthews PA, Lee JY, Alarcón GS. Nutrient intake patterns, body mass index, and vitamin levels in patients with rheumatoid arthritis. Arthritis Care Res 1997;10:9–17.
25 **Symmons DPM**, Bankhead CR, Harrison BJ, Brennan P, Barrett EM, Scott DGI, *et al*. Blood transfusion, smoking and obesity as risk factors for the development of rheumatoid arthritis: results from a primary care-based incident case-control study in Norfolk, England. Arthritis Rheum 1997;40:1955–61.
26 **Wallberg-Jonsson S**, Ohman ML, Dahlqvist SR. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in northern Sweden. J Rheumatol 1997;24:445–51.
27 **Darlington LG**, Ramsey NW, Mansfield JR. Placebo-controlled, blind study of dietary manipulation therapy in rheumatoid arthritis. Lancet 1986;i:236–8.
28 **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.