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A vegan diet free of gluten improves the signs and symptoms of rheumatoid arthritis: the effects on arthritis correlate with a reduction in antibodies to food antigens

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Abstract

Objective. Whether food intake can modify the course of rheumatoid arthritis (RA) is an issue of continued scientific and public interest. However, data from controlled clinical trials are sparse. We thus decided to study the clinical effects of a vegan diet free of gluten in RA and to quantify the levels of antibodies to key food antigens not present in the vegan diet.

Methods. Sixty-six patients with active RA were randomized to either a vegan diet free of gluten (38 patients) or a well-balanced non-vegan diet (28 patients) for 1 yr. All patients were instructed and followed-up in the same manner. They were analysed at baseline and after 3, 6 and 12 months, according to the response criteria of the American College of Rheumatology (ACR). Furthermore, levels of antibodies against gliadin and β-lactoglobulin were assessed and radiographs of the hands and feet were performed.

Results. Twenty-two patients in the vegan group and 25 patients in the non-vegan diet group completed 9 months or more on the diet regimens. Of these diet completers, 40.5% (nine patients) in the vegan group fulfilled the ACR20 improvement criteria compared with 4% (one patient) in the non-vegan group. Corresponding figures for the intention to treat populations were 34.3 and 3.8%, respectively. The immunoglobulin G (IgG) antibody levels against gliadin and β-lactoglobulin decreased in the responder subgroup in the vegan diet-treated patients, but not in the other analysed groups. No retardation of radiological destruction was apparent in any of the groups.

Conclusion. The data provide evidence that dietary modification may be of clinical benefit for certain RA patients, and that this benefit may be related to a reduction in immunoreactivity to food antigens eliminated by the change in diet.

KEY WORDS: Rheumatoid arthritis, Vegan diet, ACR response, Food antigens.

Dietary manipulation is commonly used among rheumatoid arthritis (RA) patients despite the relative lack of data from controlled studies of these regimens. Various vegetarian diets including the most pure one, i.e. the vegan diet free of gluten, are particularly popular.

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Only a few systematic studies have, however, previously addressed the issue of vegetarian food in RA. The vegan diet has been evaluated in one open study which determined the improvement in certain subjective symptoms after 3 months of the diet [1] and in one more recent controlled study in which dietary elimination combined with a vegan diet free of gluten for 3 months followed by lactovegetarian food gave a significant improvement in signs and symptoms of RA as compared with a control, non-vegetarian diet [2, 3]. These latter studies, however, not only provided support for

a positive effect of these diets on RA, but also left a number of unanswered questions concerning which features of the mixed and individualized diets caused these effects.

The objective of the present study was primarily to investigate whether a well-defined diet consisting of vegan food free of gluten could yield an improvement in signs and symptoms measured by the American College of Rheumatology (ACR) response criteria (ACR20). A secondary endpoint was if the vegan diet affected radiological signs of joint destruction in RA. Furthermore, we analysed whether eventual clinical effects could be linked to changes in immune reactions to key antigenic molecules present in milk and gluten.

Patients and methods

Patients

Sixty-six patients with RA according to ACR criteria [4] were enrolled in the study. They were eligible for inclusion if they were between 20 and 69 yr, had a disease duration between 2 and 10 yr, had not tried dietary manipulation earlier, did not have a history of food sensitivity or food allergy and had active disease. Furthermore, they should be on stable doses of non-steroidal anti-inflammatory drugs, oral glucocorticosteroids ($\leq$ 7.5 mg prednisolone) and disease-modifying anti-rheumatic drugs (DMARDs). All patients additionally received 1 mg/day vitamin B12 and 50 μg/day selenium in order to prevent dietary deficiency.

The patients were randomized to receive either a vegan diet free of gluten or a non-vegan diet for 1 yr. The patients were not informed which diet they received until after the first examination. The study protocol was approved by the local ethics committee.

Study diets

Vegan diet free of gluten (vegan diet). Thirty-eight patients were randomized to the gluten-free vegan diet which contained vegetables, root vegetables, nuts and fruits. As gluten was not permitted, the diet contained buckwheat, millet, corn, rice and sunflower seeds. Unshelled sesame seeds in the form of sesame milk was a daily source of calcium.

Well-balanced diet (non-vegan diet). Twenty-eight patients were randomized to a well-defined non-vegan diet [5]. This implies a variety of foods from all food groups according to previously described recommendations [6, 7].

For each group the new diet was introduced during an initial week of instruction in the theory and practical preparation of the diet in question by a dietitian.

Dietary intake follow-up. Each patient had access to advice and help from one of two physicians, dietitians and nurses in maintaining their respective diet. Compliance with the dietary treatment was assessed by dietary intake records.

Assessments

Improvement for each individual patient was primarily defined by ACR20 response criteria and also from changes in the individual measures contained in these criteria [8, 9].

Antibodies against food-related antigens. Immunoglobulin G (IgG) and IgA antibody levels against gliadin and β-lactoglobulin were analysed utilizing an in-house enzyme-linked immunosorbent assay (ELISA) method. Sera were initially diluted 1:50. As a reference group, 80 sera from healthy adult control subjects were investigated.

Radiographic assessment. Radiographs of hands, wrists and feet were evaluated at enrolment and after 6 and 12 months, using the modified Larsen score [10]. Furthermore, the number of erosions was calculated as well as the number of eroded joints, the joint count. X-rays were read in chronological order by a blind observer (LL).

Statistical analysis

Two groups of patients were identified for analysis in both diet groups: one intention to treat (ITT) group and a valid compliant completer (VCC) group. The ITT group included all patients randomized to one of the diets who had participated in the first week of diet instruction and at least one of the post-baseline analyses of the primary efficacy variables (after 6 or 12 months). The VCC group included the patients who had followed the trial diet for at least 9 months and had the efficacy variables performed after 12 months. Non-parametric methods were applied for statistical analyses. The Wilcoxon signed rank test was employed to perform paired comparisons for related samples and the Mann–Whitney test was used for independent samples.

Results

The two diet groups, vegan and non-vegan, were well matched at entry concerning age [49.5 (9.6) *vs* 50.8 (11.9) yr], disease duration [5.2 (2.5) *vs* 5.8 (2.8) yr], rheumatoid factor positivity (78.9 *vs* 75.0%) and treatment with DMARDs.

Twenty-two patients (57.9%) in the vegan group and 25 patients (89.3%) in the non-vegan group completed at least 9 months of their diet (VCC population).

Six of the patients in the vegan group and three in the non-vegan group had their DMARD treatment changed during the study. None of these patients belonged to the diet responders. Furthermore, intra-articular injections with glucocorticosteroids were given to 60% of the patients in the vegan group and to 82% in the non-vegan group.

The response rate at ACR20 for individual patients was higher in the vegan diet group than in the non-vegan diet group, with accumulation in the VCC group. Thus, nine of the 22 VCC patients (40.9%) in the vegan group were categorized as diet responders compared

with one of the 25 VCC patients (4.0%) in the non-vegan group after 12 months (Table 1).

Analyses of separate disease activity outcome measures contained within the ACR response criteria revealed that the vegan diet patients, as calculated on the basis of ITT, exhibited significant improvement in all variables except C-reactive protein (CRP). For vegan diet responders, CRP also improved significantly, from 24.9 (31.3) at baseline to 11.8 (16.0) mg/l at month 12 ($P < 0.05$). However, the non-vegan diet patients only had improvement in swollen joints and physician global assessment of disease activity.

The levels of IgG and IgA anti-gliadin and anti-β-lactoglobulin antibodies were not significantly different at study commencement for the two diet groups, and none of the patients had IgG or IgA deficiency. However, in the longitudinal follow-up, significant reductions in IgG anti-gliadin and anti-β-lactoglobulin levels from baseline were noted in the vegan diet group (Table 2). When subdividing the vegan group according to clinical response, this reduction in antibody levels was only significant in the responder subpopulation. In the non-vegan group, no reduction in IgG antibodies was recorded. Total IgG and IgA did not change at any time point for either of the diet groups.

Radiographic progression

After 6 and 12 months, significant increases in the modified Larsen score, the number of erosions and the joint count were observed in both diet groups. The radiographic progression was not different in the respective groups.

Discussion

This is the first controlled study to demonstrate a long-term (1 yr) effect of a vegan diet free of gluten on signs and symptoms of RA. In addition, a decrease in serum levels of IgG antibodies to gliadin and β-lactoglobulin was selectively recorded in the group of patients who responded positively to the vegan diet.

Studies of disease modification secondary to behavioural changes such as alteration of diet are faced with a number of inevitable difficulties. We made extensive efforts to avoid expectation biases by giving the patients in the two diet groups identical introductory and follow-up programmes. We also avoided providing any prior information to the patients as to which diets were to be investigated, a fact which may have contributed to the fact that so many patients in the vegan group did not complete the full 12-month diet period. Conversely, the emergence of this high rate of drop-outs in the vegan diet group indicated that the patients recruited to the study did not have a large pre-conceived preference for a vegan diet.

A significantly better result in all clinical variables included in the ACR20 index was recorded in the vegan group as compared with the non-vegan group, using both ITT and VCC modes of analysis. These findings indicate that the vegan diet may indeed have positive effects on the signs and symptoms of RA. The lack of difference between the two groups considering the radiological outcome obviously means that the vegan diet does not have any major protective effect against joint destruction. Given the limited size of the groups and the fact that many patients had advanced destruction at study entry, the power of the radiological analysis is, however, rather limited.

The positive effects of a vegan diet free of gluten on the signs and symptoms of RA observed in the present 1-yr study extend in an interesting way the observations from the study previously published by Kjeldsen-Kragh *et al.* [2], in which RA patients were subjected to a more individualized vegan diet for 3 months. In that previous study it was not possible to discern whether and to what extent the strict vegan diet was of importance for the response, as several food items were individually introduced during the study.

More importantly, no previous study has provided any clear hypothesis concerning the mechanism(s) potentially responsible for the putative positive effects of the vegan diets. The present observation of a significant decrease in both IgG anti-gliadin and IgG anti-β-lactoglobulin antibodies in the ACR20 responder group, but not in other patients, emphasizes that this decrease did not always occur as a result of a lack of exposure to the antigens. It rather suggests that a positive effect of a vegan diet in a subgroup of RA patients may indeed be due to a diminished immune response to exogenous food antigens. However, we cannot exclude that the improvement was just associated with the decrease in antibody levels with no causal connections. Furthermore, it should be pointed out that healthy persons may also have antibodies against food items, so the mere existence of food antibodies does not indicate disease.

In some earlier studies, subgroups of RA patients have been found to have elevated levels of IgG

TABLE 1. Individual responses for patients on a gluten-free vegan diet or a non-vegan diet according to ACR20 response criteria

	Vegan diet			Non-vegan diet		
	3 months	6 months	12 months	3 months	6 months	12 months
Patients, ITT (*n*)	38	38	35	28	28	26
Patients, VCC (*n*)	22	22	22	25	25	25
Patients showing 20% improvement, VCC/ITT (*n*)	6/8	10/13	9/12	1/1	2/2	1/1
%, VCC/ITT	27.3/23.7	45.5/31.6	40.9/34.3	4/3.6	8/7.1	4/3.8

TABLE 2. Anti-gliadin and anti-β-lactoglobulin antibodies in patients treated with non-vegan and vegan diets

	IgG anti-gliadin					IgA anti-gliadin				
	Baseline median values	3 months median values	0–3 months no. of patients increasing/ decreasing	12 months median values	0–12 months no. of patients increasing/ decreasing	Baseline median values	3 months median values	0–3 months no. of patients increasing/ decreasing	12 months median values	0–12 months no. of patients increasing/ decreasing
Non-vegan diet (total group)	5.5	6.5 $P = 0.0120$ [+]	13/4	6 NS	13/8	14.5	15 NS	11/14	12.5 $P = 0.0201$ [+]	15 8
Vegan diet (total group)	5	3 NS	3/14	2 $P = 0.0183$ [−]	1/12	15	13.5 NS	11/9	15 NS	9/11
Vegan diet (20% responders)	5	3 $P = 0.0254$ [−]	1/10	1 $P = 0.0071$ [−]	0/9	19	19 NS	5/8	15 NS	5/8
Vegan diet (non-responders)	3	3 NS	2/4	2 NS	1/3	10	11 $P = 0.0478$ [+]	6/1	8.5 NS	4/3
	IgG anti-β-lactoglobulin					IgA anti-β- lactoglobulin				
Non-vegan diet (total group)	3.45	3.4 $P = 0.0204$ [+]	17/6	2.9 NS	12/14	10.75	10.05 NS	14/14	8.7 NS	15 12
Vegan diet (total group)	3.25	2.6 $P = 0.0036$ [−]	10/22	3.4 $P = 0.0162$ [−]	11/22	6.65	6.6 NS	18/16	6.3 NS	15 15
Vegan diet (20% responders)	5.6	3.8 $P = 0.0066$ [−]	5/14	3.6 $P = 0.0105$ [−]	5/15	10.3	7.3 NS	8/12	6.8 NS	8/12
Vegan diet (non-responders)	2.4	2.4 NS	5/8	1.9 NS	6/7	4.8	5.9 NS	10/4	5.8 NS	7/3

For time points after baseline, P values are given for changes since baseline. Signs within brackets ([+] and [−]) denote a significant increase or decrease. Values are presented as arbitrary units/ml (U/ml). Reference values are <20 U/ml for IgG anti-gliadin, <50 U/ml for IgA anti-gliadin, <14.5 U/ml for IgG anti-β-lactoglobulin and <30 U/ml for IgA anti-β-lactoglobulin. NS = not significant. Values for anti-gliadin antibodies are given in integers, while values for anti-β-lactoglobulin antibodies are given with one valid decimal figure. Individuals not included in the columns for numbers of patients increasing or decreasing in antibody levels with time had either equal values on two occasions or values under the detection limit of the assay on both occasions.

antibodies against gliadin compared with controls [11, 12]. Increased antibody levels to several dietary antigens have also been demonstrated by Kjeldsen-Kragh *et al.* [13] in RA patients who subsequently responded favourably to a vegetarian diet. In that study, the investigators did not notice any reduction in antibody titres to dietary antigens during the vegetarian diet. In two other studies using elimination diets rather than vegetarian diets, the elimination of certain food items led to an improvement of subgroups of RA patients [14, 15]. Taken together, these studies thus provide additional support to the concept that changes in the gut immune system can influence the course of joint inflammation in RA. Further knowledge of the mechanisms behind such interactions between the gut and the joints in arthritis is needed, however, before the therapeutic potentials of this interplay can be used in a rational way in the clinic.

In conclusion, the present and earlier studies [2–3, 13] lend some support to the notion of a beneficial effect of vegetarian diets in at least some patients with RA. As such therapies are frequently adopted by RA patients, often without communication with their doctors, we hope that the results from the current study will also encourage an increased appreciation and clinical evaluation of the dietary therapies actually used by our patients.

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