

Rheumatoid arthritis treated with vegetarian diets^{1,2}

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ABSTRACT The notion that dietary factors may influence rheumatoid arthritis (RA) has been a part of the folklore of the disease, but scientific support for this has been sparse. In a controlled, single-blind trial we tested the effect of fasting for 7–10 d, then consuming an individually adjusted, gluten-free, vegan diet for 3.5 mo, and then consuming an individually adjusted lactovegetarian diet for 9 mo on patients with RA. For all clinical variables and most laboratory variables measured, the 27 patients in the fasting and vegetarian diet groups improved significantly compared with the 26 patients in the control group who followed their usual omnivorous diet throughout the study period. One year after the patients completed the trial, they were reexamined. Compared with baseline, the improvements measured were significantly greater in the vegetarians who previously benefited from the diet (diet responders) than in diet nonresponders and omnivores. The beneficial effect could not be explained by patients' psychologic characteristics, antibody activity against food antigens, or changes in concentrations of prostaglandin and leukotriene precursors. However, the fecal flora differed significantly between samples collected at time points at which there was substantial clinical improvement and time points at which there were no or only minor improvements. In summary, the results show that some patients with RA can benefit from a fasting period followed by a vegetarian diet. Thus, dietary treatment may be a valuable adjunct to the ordinary therapeutic armamentarium for RA. *Am J Clin Nutr* 1999;70(suppl):594S–600S.

KEY WORDS Rheumatoid arthritis, fasting, vegetarian diet, vegan diet, diet therapy, fecal flora, food allergy, placebo effect, eicosanoid precursors, nutritional status, humans

INTRODUCTION

Physicians as well as patients have been intrigued with the possibility that some foods can aggravate and others ameliorate the symptoms of rheumatoid arthritis, but scientific support for this view has been sparse. In this article I endeavor to summarize previously published results regarding dietary treatment of rheumatoid arthritis with particular reference to the use of vegetarian dietary regimes.

CASE REPORTS SUGGESTING AN ASSOCIATION BETWEEN DIET AND ARTHRITIS

Several anecdotal reports have suggested that there is a close relation between the diet of arthritis patients and disease activ-

ity (reviewed in 1). A variety of food items have been reported to have adverse effects, and food allergy or intolerance has been suggested as a pathogenic factor in some arthritis patients. In most cases, however, patients have either not been challenged with the suspected food items or the food challenges have not been blind. Thus, the results of these studies do not rule out the possibility that the adverse reaction to the food items was due to psychologic mechanisms, ie, pseudoallergies (2). It has become widely accepted that double-blind food challenges are necessary to identify patients with genuine food allergies or intolerance (3), but this method has only been applied in more recent trials (4–6). Although some of these studies proved that foods truly can exacerbate arthritis in some patients, it is probable that food allergies or intolerance cause disease exacerbation only rarely in arthritis patients (5, 7).

SPECIFIC DIETS FOR RHEUMATOID ARTHRITIS PATIENTS

The possible benefits of specific diets for patients with rheumatoid arthritis have been tested in several trials, but the conclusions drawn from these are conflicting. Furthermore, many of the studies that revealed positive results of dietary therapy were not published in peer-reviewed journals (8). This may be because the studies lacked controls, were poorly designed, were inadequately described, or a combination of these factors. Different diets were used in the studies so the results are not directly comparable. Most of the diets tested were vegetarian or had a limited meat content.

There has been little scientific interest in the dietary treatment of rheumatoid arthritis. One reason for this may be the considerable methodologic problems associated with clinical trials aimed at evaluating the effects of a particular diet. First, compliance is more difficult to verify than in drug trials, and second, it is extremely difficult to implement a double-blind protocol in such trials. Only Panush et al (9) have carried out a double-blind, clinical trial of a diet for rheumatoid arthritis patients. The experimental diet excluded certain food items and the placebo diet included these food items but excluded other foods. Thus, both

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TABLE 1
Food items allowed during the trial after the fasting period¹

	Strict gluten-free vegan diet (3.5 mo)	Lactovegetarian diet (12 mo)
Vegetables	All vegetables except tomatoes and cucumbers	All vegetables
Root vegetables	Potatoes, carrots, turnips, and beets	Same as the vegan diet
Fruits	All kinds of dried fruit, fresh pears, peaches, bananas, and melon	All kinds
Grain	Millet, buckwheat, rice cornflower, and cornstarch	All kinds
Seeds	Sunflower seeds, linseeds, sesame seeds, and pumpkin seeds	Same as the vegan diet
Oils	All kinds	Same as the vegan diet
Lentils	All kinds	Same as the vegan diet
Dairy products	None	All kinds of milk and dairy products
Beverage	Herb teas, vegetable broths, and decocted vegetables	Same as the vegan diet plus tea, fruit juices, and alcoholic beverages, except for red wine
Sweets	Honey and small amounts of brown sugar	Same as the vegan diet

¹From reference 10.

groups of patients were put on an exclusion diet. It is also essential, to ensure that such a diet study is truly blind, that the experimental diet not be described in books or the lay press. Otherwise, many patients would easily be able to discover whether they were following the experimental or the placebo diet.

FASTING AND VEGETARIAN DIETS FOR RHEUMATOID ARTHRITIS PATIENTS

The disparity between the numerous reports of positive effects of vegetarian diets by patients with rheumatoid arthritis and the lack of scientific foundation for this kind of therapy inspired us to carry out a comprehensive clinical trial evaluating the effect of a vegetarian diet in rheumatoid arthritis patients with active disease. This study, which will be referred to frequently in this section, was a 13-mo, prospective, randomized, placebo-controlled, single-blind trial (the examiner was unaware of the results of the randomization) (10).

After the patients consented to participate in the study they were randomly assigned to either an experimental diet group ($n = 27$ patients) or a control group ($n = 26$ patients). Patients in the experimental diet group were sent to a health farm (Tonsåsen/Nystølen Rekreasjonsheim, Etnedal, Norway) for 4 wk. The treatment was initiated by a period of fasting followed by an individually adjusted vegetarian diet. After the patients returned home and during the remaining 12 mo of the study they continued to follow their assigned vegetarian diet. The patients in the control group were sent to a convalescent home for 4 wk (Frydenberg Rekonvalescenthjem, Vikersund, Norway), where they followed an ordinary omnivorous diet that they continued to follow at home for the remaining study period. Except for the diet, all aspects of the study at the health farm and the convalescent home were comparable. Immediately before the patients went to the health farm or convalescent home and after 1, 4, 7, 10, and 13 mo, a clinical examination was performed by the present author and blood samples were taken. On the same occasions and after 2.5, 5.5, 8.5, and 11.5 mo, 24-h dietary recalls were obtained by a dietitian. Although the patients in the control group followed their usual diet throughout the study, the 24-h dietary recalls were also carried out carefully for the control group to make all conditions, apart from the diet, as equal as possible for the 2 treatment groups.

The treatment given to the experimental group during the first 4 mo was based on a dietary regimen that had been used at Tonsåsen/Nystølen Rekreasjonsheim for many years. It was modified

slightly to make it suitable for a clinical trial. During the first 7–10 d the patients fasted. There is ample scientific evidence that fasting is beneficial for patients suffering from rheumatoid arthritis (11–13) and it was thought that an immediate reduction in disease activity induced by fasting would encourage the patients to persevere with an entire year of dietary restrictions. Dietary intake during the fast consisted of herbal teas, garlic, vegetable broth, decocted potatoes and parsley, and the juices of carrots, beets, and celery. No fruit juices were allowed. The energy intake during the fast varied between 0.80 and 1.26 MJ/d.

After the fast, the patients were provided with a basic diet that consisted of the same vegetables that were used in the form of juice and broth during the fast (potatoes, carrots, celery, parsley, and beets). Because elimination diets have been used with success in rheumatoid arthritis patients (14–17), a similar principle was applied in this study. In addition to the basic diet, the patients introduced a new food item every second day. If they noticed increased pain, stiffness, or joint swelling within 2–48 h, the food was omitted from the diet for ≥ 7 d before being reintroduced. If symptoms exacerbated again, the food item was excluded from the diet for the rest of the study.

In accordance with normal practice at the health farm, the patients were not allowed to have dairy products or gluten-containing foods after the fasting period. Both of these food categories were previously reported to aggravate rheumatoid arthritis (5, 18–21). In addition, patients were not permitted to eat foods that contained meat, fish, eggs, refined sugar or citrus fruits. Salt, strong spices, and preservatives were also avoided, as were alcoholic beverages, tea, and coffee (Table 1).

The vegan diet was restricted to only 3.5 mo after the fast, after which time the patients were allowed to consume milk, other dairy products, and gluten-containing foods. However, these food items were introduced one at a time, and they were again excluded from the diet if they repeatedly exacerbated arthritis symptoms.

Some of the patients met their nutritional need for vitamin D by taking cod liver oil, and those who did not were advised to supplement their diet with vitamin D. Patients were also encouraged either to drink milk made of sesame seeds or to take other forms of calcium supplementation.

We did not monitor compliance by any objective means. During the 4 wk at the health farm it would have been difficult for the patients to diverge from the prescribed diet because they were living in a fairly closed community lacking dietary temptations. After they returned home there was no assessment of

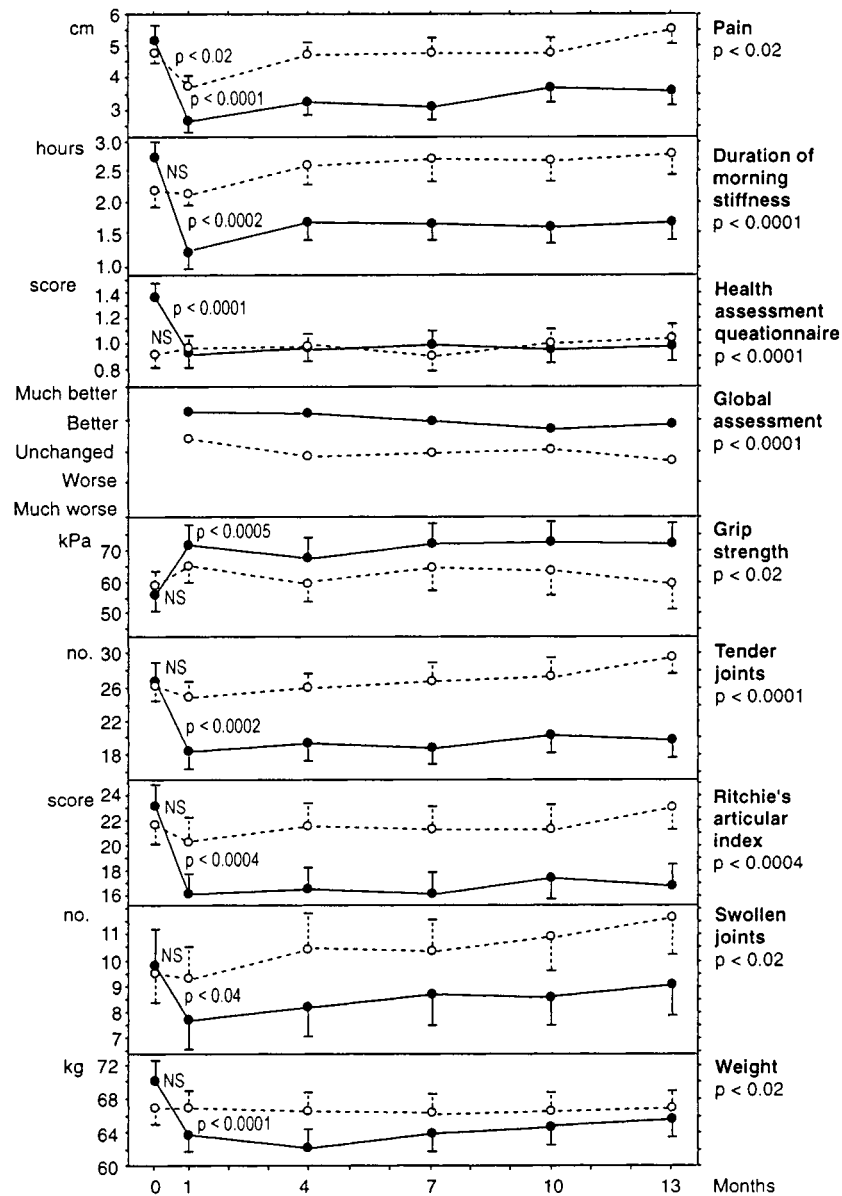


FIGURE 1. Mean \pm SE values of clinical variables as measured at each clinical examination in the experimental diet group (●), and the control group (○). SEs for global assessment were too small to be depicted on the figure. The *P* values inside the boxes refer to the differences between the values at baseline and after 1 mo of treatment. For pain, *P* value outside the box refers the result of an unpaired *t* test of the endpoint values; other *P* values outside the boxes refer to the results of testing for significant overall differences between vegetarians and omnivores. ANOVA models in which the dietary treatment (vegetarian or omnivorous diet) was considered as the main effect (overall difference) were used for these comparisons. Reprinted with permission from reference 10.

compliance apart from the 9 occasions when the dietitian obtained 24-h dietary recalls.

Clinical responses to vegetarian diet

The mean of almost all disease activity variables decreased significantly in the experimental diet group after 1 mo of treatment (Figures 1 and 2). Furthermore, the overall change in most of these variables also favored the experimental diet group compared with the omnivorous control group (10, 22). From a clinical point of view, however, a statistically significant difference between 2 groups does not necessarily mean that the difference in individual

patients is of any clinical value. Therefore, patients were divided into "responders" and "nonresponders" according to certain clinical criteria (23). We found that 12 of the 27 patients in the experimental diet group showed significant clinical improvement compared with only 2 of the 26 patients in the control group ($P < 0.003$, Fisher's exact test).

After the study, the patients were free to change their diets or medications. One year after completion of the trial, 22 patients from the experimental diet group and 23 omnivorous control subjects were reexamined (24). Patients who were categorized as diet responders according to the outcome of the initial trial were com-

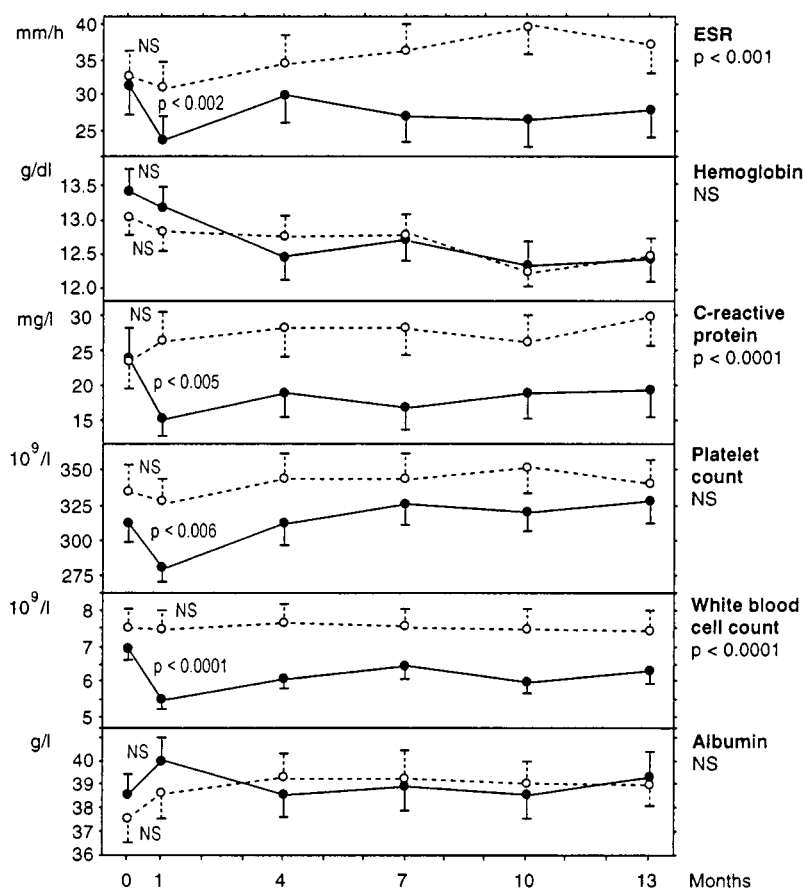


FIGURE 2. Mean \pm SE values of laboratory variables as measured at each clinical examination in the experimental diet group (●) and the control group (○). *P* values inside the boxes refer to the differences between the values at baseline and after 1 mo of treatment. *P* values outside the boxes refer to the results of testing for significant overall differences between vegetarians and omnivores. ANOVA models in which the dietary treatment (vegetarian or omnivorous diet) was considered as the main effect (overall difference) were used for these comparisons. Reprinted with permission from reference 10. ESR, erythrocyte sedimentation rate.

pared with the diet nonresponders and omnivorous control subjects. The most pronounced improvement compared with baseline was observed in the diet responders. The differences between the 3 groups were significant for most of the clinical variables but not for the laboratory variables. At the time of the follow-up examination all of the diet responders, but only half of the diet nonresponders, were still following the diets they had consumed during the trial.

MECHANISMS THAT MAY EXPLAIN THE EFFECT OF VEGETARIAN DIET

Psychobiological mechanisms

Because the trial was single-blind, it is possible that the difference in the clinical course between the 2 groups was due to psychobiological factors or a placebo effect. To disclose the importance of such matters, we assessed several psychological characteristics of the patients before they were randomly assigned to groups (23). Most of these variables did not differ between diet responders and nonresponders, but the diet responders were found to believe less in the effect of ordinary medical treatment than the diet nonresponders. This difference in expectancy may

indicate that a placebo effect could have contributed to the clinical improvement observed in the diet responders. It is not likely, however, that a placebo response alone can explain the effect of a vegetarian diet. The placebo effect usually declines gradually over time and, hence, it is difficult to comprehend why the clinical improvement obtained during the study was still present 1 y after the patients had completed the trial. Furthermore, we found clear, objective signs of decreased disease activity in the diet responders. In contrast, placebo treatment (25) as well as psychologic treatment (26) aimed at improving the ability of rheumatoid arthritis patients to cope with arthritis reduces only subjective disease activity variables.

Immunosuppression due to decreased energy intake

Restricting the intake of energy, proteins, or certain vitamins and minerals is known to suppress various aspects of the immune response (27). Because immunosuppression is an effective and widely used treatment of autoimmune diseases, it is relevant to ask whether the beneficial effect of the vegetarian diet in the present study was due to immunosuppression secondary to malnutrition. Correlations between clinical improvement and changes in lean body mass could not be carried out because the latter variable was

not assessed. However, total weight reduction over time did not differ significantly between diet responders and nonresponders. This result agrees with those of 2 other studies (17, 28).

Food allergy or intolerance

Because food allergies and intolerance have been suggested to play a role in the pathogenesis of some patients with rheumatoid arthritis, we measured immunoglobulin (Ig) E, IgG, IgM, and IgA antibody concentrations against antigens in foods often reported to aggravate arthritis symptoms. At the start of the trial, 13 of the 27 patients in the vegetarian diet group considered themselves to have a food allergy and at the end of the trial 10 patients thought that they could identify foods that caused a flare-up of symptoms (10). However, there was no association between the food items that were claimed to give rise to adverse reactions and the antibody activity against antigens in these foods (29). Moreover, in patients who had high levels of antibody activity against certain food antigens, the fluctuations in antibody activity did not correspond with changes in the clinical variables. Altogether, the data did not indicate that systemic immune reactions against food antigens are of major pathogenic importance in most patients.

Eicosanoid precursors

Alterations in the proportions of the various fatty acids in the diet give rise to changes in the profiles of the fatty acids in the phospholipids of the cell membranes, and an omnivorous diet differs considerably from a vegetarian diet in this respect (30, 31). Because some of these fatty acids are precursors of proinflammatory prostaglandins and leukotrienes, a switch from an omnivorous to a vegetarian diet could bring about changes in phospholipid profiles that could influence the inflammatory process. Concentrations of phospholipid fatty acids were therefore measured in the experimental diet groups, and changes in concentrations were related to clinical variables (32). Significant changes in the concentration of several fatty acids could be observed when omnivorous patients consumed the vegan diet and also when they switched to the lactovegetarian diet. The fatty acids concentrations, however, did not differ significantly between diet responders and nonresponders, so that the clinical effect of a vegetarian diet does not seem to be due to changes in eicosanoid precursor concentrations. This finding agrees with those of previous trials in which there were only modest clinical effects of more direct methods of manipulating fatty acids, eg, by supplementing the diet with either fish oil or evening primrose oil (8).

Is there a role for *Proteus mirabilis* in the pathogenesis of rheumatoid arthritis?

Proteus mirabilis is a normal, commensal component of the human bowel flora and a common cause of urinary tract infections. This organism has been suggested to be involved in the etiopathogenesis of rheumatoid arthritis (33–35). A surface-membrane hemolysin of *P. mirabilis* contains a sequence of 6 amino acids, ESRRAL (glutamic acid, serine, arginine, arginine, alanine, and leucine), that closely resembles a sequence, EQRRAA (glutamic acid, glutamine, arginine, arginine, alanine, and alanine), that is present on the β -chain of the human leukocyte antigen (HLA) DR1 molecule and on the HLA-DR4 subtypes known to be associated with rheumatoid arthritis. Antibody activity against a 16-mer synthetic peptide containing the ESRRAL sequence has been found to be significantly higher in rheumatoid

arthritis patients than in patients with ankylosing spondylitis or in healthy control subjects (36). Similar differences were also detected for antibody activity against the native *Proteus* hemolysin protein. In a related study, autoantibodies against a 16-mer synthetic peptide of the β -chain of the HLA-DR4/DW15 molecule, containing the EQRRAA sequence, were reported to be elevated in Japanese patients with rheumatoid arthritis (37). Thus, it is conceivable that *Proteus* antibodies with specificity against the ESRRAL sequence can cross-react with cells expressing the HLA-DR β -chains containing the EQRRAA sequence. These antibodies may in turn initiate or perpetuate the inflammation by activating the complement cascade or stimulating natural killer cells.

Antibody activity against *P. mirabilis* was therefore measured in serum samples from the patients who participated in the trial of fasting and vegetarian diet. The change to a vegetarian diet caused a significant decrease in IgG antibody activity against *P. mirabilis* (38). The decline was significantly more pronounced in the diet responders than in the nonresponders and omnivores (Figure 3). Furthermore, this decline correlated significantly with a decline in a composite index of disease activity. In contrast, antibody activity against *Escherichia coli* showed no change in response to dietary treatment nor did it correlate with changes in disease activity. These results suggest an attenuation of the IgG immune response against *P. mirabilis* but not against *E. coli* during treatment with a vegetarian diet. This may be due to reduced stimulation of the immune system by *Proteus* antigens. The immune stimulation could either have derived from bacteria in the genitourinary system or from the microflora of the gut.

Changes in the fecal flora

The total surface area of the gastrointestinal system is $\approx 300\text{--}400\text{ m}^2$. Only a single layer of epithelial cells separates the individual from enormous amounts of antigens of both dietary and microbial origin. The gut-associated lymphoid tissue, which comprises the largest lymphoid organ of the body, protects the individual from harmful antigens that pass through the epithelial layer. Therefore, a change in the fecal flora that alters the antigenic challenge of the gut may influence the degree of joint inflammation in patients with rheumatoid arthritis.

Three decades ago Olhagen and Månsson (39) found the *Clostridium perfringens* flora in the feces of rheumatoid arthritis patients to be qualitatively and quantitatively abnormal. These findings are intriguing in the context of dietary modulation of rheumatoid inflammation because these same authors and others were able to induce arthritis in pigs by feeding them dry fish powder only (40). The arthritis, which was very similar to rheumatoid arthritis, was also associated with an increase in fecal *C. perfringens*.

These results were achieved by traditional bacteriologic techniques, ie, isolation, identification, and enumeration of different bacterial species in the stool samples. Analysis of bacterial-fatty acid profiles produced by gas-liquid chromatography has proved to be a more sensitive method for detecting changes in the microflora composition (41). Application of this method to the fecal samples obtained from the patients who participated in the trial of fasting and vegetarian diet showed convincingly that the bacterial composition of the feces was influenced by diet (42). We also applied this method to compare fecal samples obtained at times at which patients had experienced a pronounced improvement with fecal samples collected at times of little or no clinical improvement. This comparison revealed that



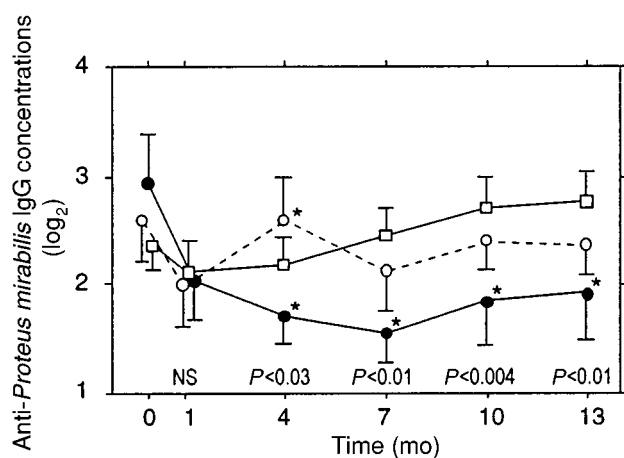


FIGURE 3. Mean \pm SE anti-*Proteus mirabilis* concentrations expressed as \log_2 units of the antibody titers as measured at each clinical examination in the diet responders (●), diet nonresponders (○), and control group (□). A value of 1 equals a titer of 20. *P* values are results of the Kruskal-Wallis test (significance level: $P < 0.05$). Significance by the Kruskal-Wallis test was followed by 3 post hoc comparisons with the Mann-Whitney *U* test (significance level: $P < 0.0167$); *significant difference from omnivorous control group at the same time point.

the 2 groups of feces samples differed, but the differences were only significant after 1 and 13 mo, and were nearly significant after 7 mo (42). In a recent study, Peltonen et al (43) found significant diet-associated changes in fecal flora in Finnish rheumatoid arthritis patients who were randomly assigned to follow an uncooked vegan diet rich in lactobacilli. In this trial they also found significant differences in the gut microflora between diet responders and nonresponders, but no attempts were made to identify which bacterial species were responsible for these differences.

These data can be interpreted in 3 ways:


- 1) The diet changes the fecal flora and thereby alters the amount and type of bacterial substances absorbed by the intestinal mucosa. The absorbed bacterial substances in turn influence the inflammatory process in the joints.
- 2) The cause-effect relation may be the opposite. Rheumatoid arthritis is a systemic disease that can affect almost all tissues, and a reduction in disease activity may also involve the intestine. Changed conditions in the bowel can in this way influence the growth conditions of the intestinal bacteria and thereby alter the balance between the different species of the microflora.
- 3) There may be a common unknown factor that is responsible for both the decreased disease activity and the changed bacterial profile of the fecal samples.

Although the 2 latter explanations cannot be excluded, the first interpretation is the most attractive. There is a clear genetic component in rheumatoid arthritis (44), but the concordance rate in monozygotic twins indicates that it is unlikely to be $>30\%$, leaving 70% to be explained by exogenous factors (45). The human colon, which contains $\approx 10^{14}$ individual bacteria (46) divided among 400–500 species (47), would be an appropriate place to search for environmental factors that influence rheumatoid inflammation.

WHAT ARE THE RISKS OF CHANGING FROM AN OMNIVOROUS TO A VEGETARIAN DIET?

Active rheumatoid arthritis is known to be associated with poor nutritional status, but it has been claimed that the dietary intake of patients with rheumatoid arthritis is not significantly different from that of healthy control subjects (48). This apparent discrepancy is explained by the higher energy expenditure in rheumatoid arthritis patients, probably caused by cytokines such as tumor necrosis factor α and interleukin 1β (49). Special attention should be paid to the hazards of malnutrition in rheumatoid arthritis patients following a vegan because of the shortage of calcium and vitamins D and B-12 in plant foods. Therefore, we monitored the nutritional status of the patients during the trial (50). There were indications of a reduction in lean body mass during the first half of the study because the upper arm muscle area of the patients in the vegetarian group was significantly lower after 1, 4, and 7 mo compared with baseline. This unfavorable effect of the dietary regimen could not be prevented despite close follow-up by the dietitian. However, the nutritional status improved after the 4th month when the patients were allowed to consume gluten-containing foods and dairy products.

CONCLUSION

Fasting followed by a vegetarian diet has a favorable influence on disease activity in some patients with rheumatoid arthritis. This effect cannot be explained entirely by psychobiologic factors, immunosuppression secondary to energy deprivation, changes in the plasma concentration of eicosanoid precursors, or changes in antibody activity against dietary antigens. Changes in disease activity were found to be associated with concurrent alterations in the fecal microflora and in the antibody activity against *P. mirabilis*. These findings may indicate that the beneficial effect of dietary treatment is caused by alterations in the microflora secondary to changes in the diet. Provided that detrimental effects on nutritional status can be prevented, dietary treatment may prove to be a valuable supplement to the ordinary therapeutic armamentarium for rheumatoid arthritis. However, more carefully controlled clinical trials are warranted before this treatment modality will gain wide acceptance. 

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