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General or personal diet: the individualized model for diet challenges in patients with rheumatoid arthritis

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Abstract This study was performed to evaluate the effect of individualized diet challenges consisting of allergen foods on disease activity in rheumatoid arthritis (RA) patients. Twenty patients with positive skin prick test (SPT) response for food extracts and 20 with negative SPT response were included. All patients were instructed to restrict the most common allergen foods during 12 days and then assigned into two groups according to SPT results. Food challenges were performed with all of the allergen foods in prick test positive group (PTPG) and with corn and rice in prick test negative group (PTNG) during 12 days. Allergen foods were then eliminated from PTPG patients' diet, while corn and rice were removed in PTNG. Clinical evaluations were performed after fasting (baseline), at the end of the challenge phase and reelimination phase. Stiffness, pain, physician's and patient's global assessment of disease activity, health assessment questionnaire (HAQ), Ritchie's index, serum amyloid A protein, erythrocyte sedimentation rate and C-reactive protein were determined. All of the disease variables, except HAQ, were increased with food challenges in PTPG. In PTNG, no significant change was observed in any of the variables except pain ($P < 0.05$) and patient's global assessment ($P < 0.05$). Our results showed that the individualized dietary manipulations may effect the disease activity for selected RA patients.

Keywords Rheumatoid arthritis · Food allergy · Food challenges · Disease activity · Skin prick test

Introduction

Food allergy may be related to rheumatoid arthritis (RA) by evoking immune responses, which are important in the pathogenesis of rheumatic diseases. However, there is evidence that diet can influence some forms of arthritis [1]. Also, the relationship between a certain food and disease activity has been recorded in the case reports with various chronic inflammatory disorders such as RA and seronegative arthritis [2, 3]. Although the dietary connection between RA and food sensitivities was known for a long time, the link between food allergy and RA symptoms and severity is complex [1]. Food allergies are usually mediated by IgE antibody directed to specific food-related proteins, but the other immunologic mechanisms and cytokines can also play an important role [4]. Acute allergic reactions, such as anaphylaxis, and chronic health problems, such as asthma, arthritis and gastrointestinal disorders may be caused or exacerbated by food allergy.

The diagnosis of food allergy requires a careful search for possible causes, including diagnostic tests to rule out other conditions and specific tests for IgE such as skin prick test (SPT), radioallergosorbent test (RAST) and oral food challenges [4]. The SPT is commonly used to identify if an allergy exists. This procedure is safe and generally not painful [5]. On the other hand, the most reliable way to determine if a food is causing an allergy or intolerance is via a rotational diet. This can be done simply by removing the suspected allergen food from the diet for a period of 7–15 days, and observing the results. The challenge period follows the elimination diet. Each suspected food is eaten in increasing amounts for at least three days in the challenge phases. If no symptoms are observed, the food being tested may stay in the subject's diet and then the next suspected food can be examined by

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the same method. However, if food-induced symptoms manifest during the challenge period, the tested food must be avoided and at least two days grace period be given before the next challenge is initiated [6]. This process takes a long time both for the patient and physician and increases economic burden of RA. Also, these procedures may affect as negative to the patients compliance for further dietary therapy. However, the collected food challenges may be performed with food items defined as allergen to decrease these negative respects. Also, SPT, which is an easy method, may be used to identify allergen foods. Dietary challenges may be experimented in patients with positive SPT response rather than with negative SPT response. Therefore, we investigated the effect of personal food challenges consisting of allergen foods on disease activity in patients with RA.

Material and methods

Patients with RA, according to the criteria of the American College of Rheumatology [7], were included in this study. The SPT with food extracts was performed in these patients for most allergen foods. Twenty RA patients with the positive SPT response for at least one food and 20 patients with the negative SPT response were included. All of the patients had a disease duration of at least two years and had functional status class I-II as defined by the American College of Rheumatology [8]. None of the patients had clinically active disease, as defined by the presence of at least two of the following criteria: (1) morning stiffness duration >30 min, (2) six or more tender joints, (3) three or more swollen joints, and (4) erythrocyte sedimentation rate (ESR) >28 mm/h. All of the patients continued their previous disease modifying antirheumatic drug medication at the beginning. Patients who had a history of dietary manipulation, antihistamines, glucocorticoids and non-steroidal antiinflammatory drugs intake for at least a month before the SPT were not included. However, paracetamol intake was not restricted during the study, except the clinical assessment days. All of the participants were hospitalized to supply the dietary compliance of patients and to prevent from disease activations due to environmental impacts. Informed consent was obtained from all patients and this study protocol was approved by the local ethics committee.

Skin prick test was applied for 31 kinds of food with extracts (Stallergenes SA, France) (Table 1). The tests of milk, dairy products and red meat were not made since these extracts were not imported due to risk of the 'bovine spongiform encephalopathy'. SPT was performed on the volar side of the forearm with commercially available food extracts. The histamine and saline solution were used for positive and negative controls. The diameters of resulting wheal and flare reactions are recorded after 15 min. A positive SPT response was defined as a wheal ≥ 3 mm larger than the negative control wheal.

Table 1 The used food extracts for the skin prick test and positive results in the 20 patients with rheumatoid arthritis

Food	Positive prick test (n)	Food	Positive prick test (n)
Wheat	8	Pea	3
Corn	7	Apple	3
Wheat flour	5	Walnut	2
Soybean	5	Almond	2
Coffee	5	Cocoa	1
Yolk	4	Rye flour	1
Orange	4	Tomato	1
Peanut	4	Banana	1
Refined sugar	4	Kiwi	1
Tea	4	Carrot	1
Chicken	4	Spinach	1
Strawberry	4	Fresh fish	1
Lemon	3	Apricot	–
Hazelnut	3	Potato	–
Egg white	3	Rice	–
Peach	3		

One patient was excluded from the study because of positive SPT for rye flour. One patient with negative SPT response was withdrawn since disease aggravation occurred due to severe urinary infection. Three patients (one subject with positive and two subject with negative SPT response) were excluded at the elimination phase owing to low diet compliance. Thirty five patients completed the study (18 with positive SPT response, 17 negative SPT response).

The elimination phase

All patients were instructed to restrict the most common allergen foods, such as dairy products, eggs, meat, fish, refined sugar, wheat, wheat flour, corn, rice, nuts, citrus fruits, tomato and coffee during 12 days. The menu was based on cooked vegetables, legumes and compote fruit and were regulated for intake of energy, fat, carbohydrates and protein by a dietitian. However, bread which is eaten as part of every meal in Turkish culture is a stable food. Therefore, rye bread without wheat flour which is known as less allergen than wheat in RA (34% and 54%, respectively) [9], was given for limited amount per day during the study.

The challenge phase

Thirty five patients were separated into two groups according to the results of the SPT after the elimination phase. Eighteen patients who had a positive response were named as prick test positive group (PTPG). For each patient, prick positive foods were added at increased amount to patient's diet in PTPG. Therefore, the diet regimen was different for each subject in the challenge phase. The patient ate all of the prick positive food every day. This personal diet was continued during the 12 days.

Seventeen patients had negative response for all of the allergen food extracts on the SPT. Increased amount of the two foods were added to patient's diet in prick test negative group (PTNG) to determine the placebo response to dietary challenge. Corn, which is known as the most allergen food in RA patients (57%), and rice which is not defined as an allergen food, were selected for this reason [9]. This diet, consisting of corn and rice, was given during the 12 days.

The reelimination phase

After the food challenges, prick positive foods for each patient were eliminated from the patient's diet in PTPG during 12 days. In PTNG, corn and rice were excluded from daily diet.

All the patients were examined for clinical and laboratory assessments after the elimination phase (baseline), at the end of challenge phase and reelimination phase. Clinical evaluations and dietary manipulations were made by different researchers. For clinical evaluation, we recorded morning stiffness, pain at rest (visual analogue scale (VAS), 0–10 cm), physician's and patient's global assessment of disease activity (five-point categorical scale, 0 = best score), health assessment questionnaire (HAQ) [10] and Ritchie's articular index [11]. In the laboratory assessment, ESR, C-reactive protein (CRP) and serum amyloid A protein (SAA) levels were measured. ESR level was determined by the Westergren method. A nephelometric method was used for measuring CRP levels (Beckman Array Protein System, USA). SAA levels were defined using commercial kits (Cat. No: KHA0012, BioSource Int., USA) by ELISA method.

Statistical analysis

Statistical analysis was made by means of the SPSS 10.0 for Windows program. All of the data were examined for normality. Normally distributed data were expressed

as the mean with standard deviation, otherwise as the median with ranges. Comparison of groups with normally distributed values was performed using the unpaired samples *t* test, otherwise the Mann Whitney *U* test was applied. Paired samples *t* test and Wilcoxon-rank test were made for comparison of normally and non-normally distributed data within groups, respectively. Values with $P < 0.05$ were accepted as statistically significant.

Results

The patients in PTPG and in PTNG had an average age of 46.1 ± 8.7 and 48.4 ± 10.2 years, and average disease duration of 54 (24–240) and 48 (24–240) months, respectively. There was no statistically significant difference in the demographic analysis of two groups ($P > 0.05$). Also, at the baseline, no differences on clinical and laboratory values were observed between both groups (Table 2).

All of the clinical and laboratory variables, except HAQ, were significantly increased at the end of the challenge and reelimination phases in PTPG. During the study process, no significant difference was determined in any of variables, except pain ($P < 0.05$) and patient's global assessment ($P < 0.05$) in PTNG. However, these two variables were decreased at the end of the challenge phase ($P < 0.05$) (Table 2). During the study, there were observed important differences between two groups on CRP, SAA, pain, morning stiffness, and patient's and physician's global assessment (Table 3).

In 13 patients (72%) within PTPG, an important disease aggravation was observed by the food challenges. These exacerbations disappeared in only one patient by the reelimination. In PTNG, disease activity was increased in three patients (18%) by the food challenges and continued during the reelimination. During the study, no difference was observed for body mass index between the two groups. Also, the patients had no significant weight loss in both groups at the end of the trial.

Table 2 Comparison of clinical and laboratory data at the end of challenge and reelimination phases versus baseline in both of groups (median (range))

	Prick test positive group			Prick test negative group		
	Baseline	Challenge	Reelimination	Baseline	Challenge	Reelimination
Stiffness (min)	15 (1–30)	32.5 (10–60)***	52.5 (10–120)***	15 (1–30)	10 (1–45)	10 (1–60)
Pain (VAS)	3 (1–7)	5 (1–10)**	6.5 (1–10)**	4 (2–6)	4 (1–6)*	4 (2–8)
Physician's gl. as.	1 (0–2)	1 (0–3)*	1 (0–4)**	1 (0–2)	0 (0–2)	0 (0–3)
Patient's gl. as.	1 (0–2)	2 (0–3)**	2 (0–4)**	1 (0–2)	0 (0–2)*	1 (0–3)
Ritchie's index	11.5 (5–30)	15.5 (2–57)*	16.5 (4–66)*	10 (0–33)	8 (1–32)	9 (0–34)
HAQ	3 (0–13)	4 (0–14)	4 (0–18)	3 (0–15)	4 (0–15)	5 (0–17)
SAA (ng/ml) ^a	1152.7 ± 290.2	1526.7 ± 382.7****	1497.6 ± 367.7***	1035.6 ± 163.4	1109.7 ± 252.9	1124.7 ± 340.1
CRP (mg/dl)	0.4 (0.3–0.5)	1 (0.3–5.4)***	1.2 (0.3–7.6)***	0.5 (0.3–0.5)	0.4 (0.3–1.6)	0.4 (0.3–3.8)
ESR (mm/h) ^a	20.3 ± 7.9	28 ± 15.6*	31.2 ± 14.8**	18.2 ± 6.4	21 ± 6.8	23.4 ± 12.1

Physician's gl. as: physician's global assessment, Patient's gl. as: patient's global assessment * $P < 0.05$, ** $P < 0.01$, *** $P = 0.001$, **** $P < 0.001$; Compared with baseline values, ^amean ± SD

Table 3 Comparison of significance levels in challenge and reelimination phases between two groups

	Challenge phase	Reelimination phase
Stiffness (min)	$P = 0.001$	$P = 0.001$
Pain (VAS)	$P < 0.05$	$P < 0.05$
Physician's global assessment	NS	$P < 0.05$
Patient's global assessment	$P < 0.05$	$P < 0.05$
Ritchie's index	NS	$P < 0.05$
HAQ	NS	NS
SAA (ng/ml)	$P = 0.001$	$P < 0.01$
CRP (mg/dl)	$P < 0.001$	$P < 0.01$
ESR (mm/h)	NS	NS

NS not significant

Discussion

The dietary treatment of RA is a controversial issue. A number of dietary therapy studies have investigated the effects of several dietary elimination forms on the RA symptoms. Panush et al. [12] performed a popular Dong restricted diet which eliminated dairy products, citrus fruits, tomatoes, meat and coffee in 26 patients with RA. However, they could not find any difference between diet group and control group. Skoldstam et al. [13] investigated the efficacy of a Mediterranean diet consisting of a high consumption of fruit, vegetables, cereals and legumes, versus an ordinary Western diet including more red meat and fish, on the disease activity in RA. They found a decrease in DAS 28, HAQ, swollen joint count, CRP and pain in Mediterranean diet group, despite the fact that they did not define any change in the control group. In a vegan diet free of gluten study, Hafstrom et al. [14] reported that 45% of the patients in the vegan group were responders, according to the ACR 20 improvement criteria compared with 4% in the non-vegan group. The reason for variable results in these studies may be due to administration of the same general diet forms to all of RA patients. The individualization of elimination diet may increase the improvement rate in the signs and symptoms of RA. However, there are few studies that investigate the effects of personal dietary manipulation in RA. Darlington et al. [15] made RA patients to fast for 1 week followed by food challenges. They defined as good responders the 33 patients at the end of a 6-week elimination diet which removed the foods causing the symptoms. In a double-blind study, an allergen free diet was compared with low allergen-diet containing lactoproteins and yellow dyes [16]. During the second 4-week period, patients returned to their usual diets. In both the groups, only subjective improvements were found but there was not any difference between two tested diets. Also, only 11.5% of the total patients had favourable responses, followed by marked disease aggravation during rechallenge.

In this study, a low-allergen diet from which the most common allergen foods were eliminated, was given to all RA patients for 12 days. Then the food challenges were performed with all of the allergen foods defined with SPT. We found statistically significant differences in clinical variables, except Ritchie's index and HAQ, with

the challenges in PTPG compared with the PTNG. However, serum CRP and SAA levels were found to be different between both groups, but not ESR. In RA, ESR and CRP are traditional objective laboratory markers of disease activity. In recent studies, it was reported that CRP is a great value as an inflammatory marker [17]. CRP must be considered an exact measure of the acute phase response, since ESR is additionally affected by several factors such as age, sex, anaemia and elevated fibrinogen levels [18]. Also, serum CRP levels may decline to normal values following successful treatment, while ESR levels may remain elevated during a longer period [17, 18]. On the other hand, SAA has been reported to be more sensitive than CRP as a marker of disease activity and to be the best marker available for the assessment of inflammatory joint disease [19].

On the other hand, 13 patients in PTPG experienced disease exacerbation after intake of prick positive foods. Interestingly, this aggravation did not settle at the end of reelimination phase in 12 of 13 patients. A 12-day time is generally adequate for withdrawal of most of allergen food fragments from the body. However, the clearing of body system entirely may take up to longer time for some food items. Unfortunately, each patients received different allergen foods but disease variables did not recover during the elimination in most of the patients. Therefore, it seems that food allergy may be a triggering factor rather than a causative factor in RA etiopathogenesis. The interaction of foreign food fragments with either specific or nonspecific recognition components of the immune system may stimulate the inflammatory process in RA.

On the other hand, patients with RA have spontaneous temporary remissions and exacerbation of symptoms. A proportion of the disease aggravation observed during food challenges may occur as a result of natural variations in the disease activity or as reflecting a placebo effect. However, a number of patients reported an increase in disease signs and symptoms in PTPG more than in PTNG (13 and 3, respectively). Also, objective laboratory variables were different between two groups. Therefore, the spontaneous disease aggravation and placebo effect were not sufficient exactly to explain the whole changes. The high-response rate found in this study seem due to the performing of the personal diet manipulations with private allergen foods for each patient. The allergen food items were identified by the

SPT. SPT is cheap, safe, and can be in the doctor's office. Also, the results are usually received within 15–20 min. However, SPT cannot show food intolerance in all cases. In addition, the uncontrolled effects, as vitamin E and K deficiency, low vitamin D and long-chain omega-3 fatty acids intake, may cause limitation in the study results.

In conclusion, our results suggested that the individualized dietary manipulations may effect the disease activity for selected patients with RA. However, further long-term studies investigating the effects of individualized diet therapy free from SPT positive foods on the clinical and laboratory variables in RA patients can be helpful in the development of new patient-specific treatments.

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